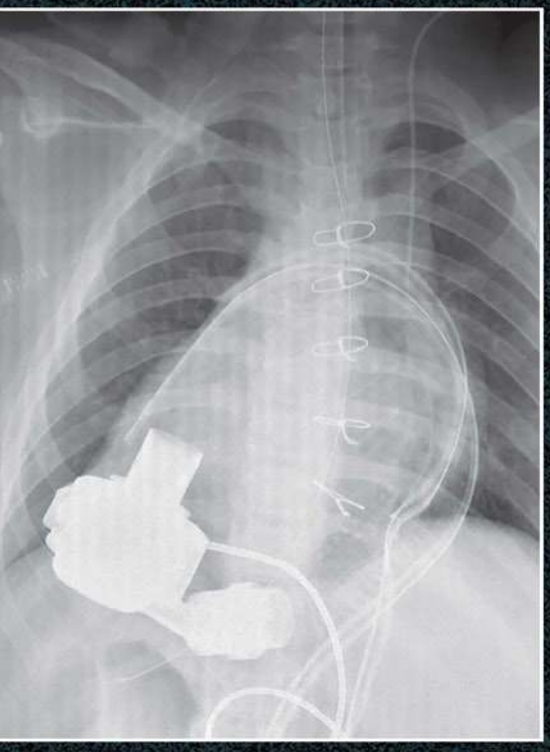
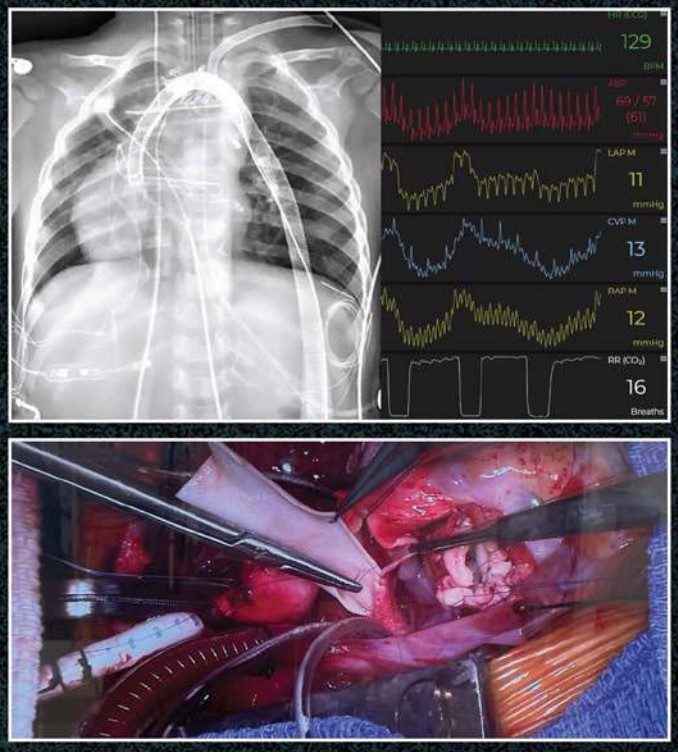
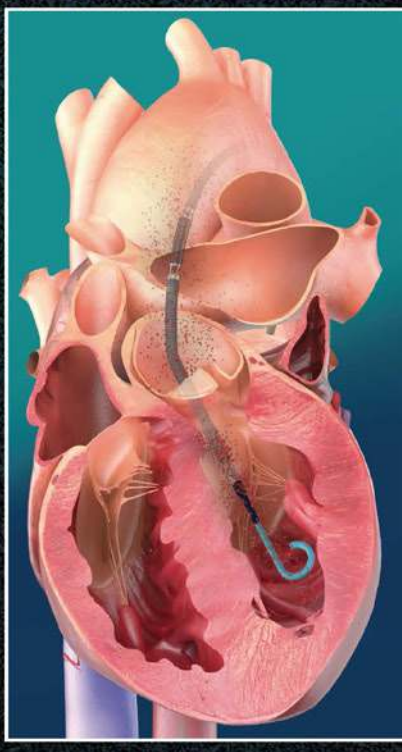
Fourth Edition

Anesthesia for Congenital Heart Disease







Editor-in-Chief: Dean B. Andropoulos
Editors: Emad B. Mossad • Erin A. Gottlieb

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Anesthesia for Congenital Heart Disease

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Preface to the Fourth Edition

In the 17 years since the first publication of *Anesthesia for Congenital Heart Disease*, each successive edition has seen a significant expansion in the material in the book due to the ongoing rapid advances in the field of congenital heart disease (CHD). The Fourth Edition marks the greatest number of changes since the conception of this book, and the new chapters and content, including thorough chapter updates and the addition of many more figures and tables that illustrate the myriad of changes in this field, are designed to further enhance the knowledge of the anesthesiologist and others caring for CHD patients. The continued participation of a number of international authors contributes to the many perspectives represented in congenital cardiac anesthesia care; it truly is a world-wide field. Chapter 4 is a new chapter entitled, "Multidisciplinary Collaboration, Team Functioning, and Communication in Congenital Cardiac Care." This chapter emphasizes the unique nature of an often large, multidisciplinary team that must work together to make complex patient care decisions, and then perform the procedures and care that result in the best possible patient outcomes. It also focuses on the role of the Congenital Cardiac Anesthesiologist, not only to provide patient care but also to make substantive contributions to clinical decision-making and leadership in the Heart Center. Another new chapter is Chapter 5, "Informatics and Artificial Intelligence in Congenital Heart Disease," which presents an overview of this crucially important field of medicine, which has a number of applications in Congenital Cardiac Anesthesia and Critical Care, and CHD in general. Chapter 8 is entirely devoted to Genetic Syndromes in CHD; an increasingly recognized and important aspect in the care of patients with CHD; it seeks to inform the anesthesiologist about the genetic underpinnings of many syndromes in CHD, their multisystem involvement, and the ethical principles of providing care for this complex population. Chapter 17 presents Point of Care Ultrasound in CHD, which has become an increasingly important skill for the Congenital Cardiac Anesthesiologist, not only to assist in vascular access procedures but also to assess the heart and lungs during procedures and emergencies to guide diagnostic and therapeutic choices. Finally, Chapter 25 is dedicated to Cardiac Arrest and Resuscitation in CHD, which has many unique features as a result of the anatomy and pathophysiology of these patients. The Key Points and Selected References are again included in all chapters, to enhance the reader's learning and provide an opportunity for further knowledge.

We are pleased to welcome as Editor Erin A. Gottlieb, M.D., M.H.C.M., our former Texas Children's Hospital colleague who is now Chief of Pediatric Cardiac Anesthesia at Dell Children's Medical Center, and the University of Texas Dell Medical School in Austin, Texas. Two editors from the Third Edition, Drs. Stephen Stayer and Wanda Miller-Hance, have retired from this role, and we wish to thank them for their many contributions to previous editions, and for their ongoing work as chapter authors for the Fourth Edition.

We would like to dedicate this edition of the book to Dolly D. Hansen, M.D. who passed away in 2021. Dr. Hansen came to Boston Children's Hospital (BCH) in 1971 for a Pediatric Cardiac Anesthesia Fellowship and spent the remainder of her career there until her retirement in 2001. Among the many firsts that Dr. Hansen was an integral part of was the establishment of the neonatal arterial switch operation as the preferred surgical strategy, the first Stage I Palliation for Hypoplastic Left Heart Syndrome, the first deep hypothermic circulatory arrest case at BCH, and landmark studies of high-dose opioid anesthesia and survival in neonatal cardiac surgery. Dr. Hansen was not only an outstanding clinician, but she also had a profound effect as a teacher of a very large group of anesthesia fellows at BCH. As one of the first female Pediatric Cardiac Anesthesiologists, Dr. Hansen paved the way for many to follow in her footsteps. Dr. Hansen was awarded the inaugural Congenital Cardiac Anesthesia Society Lifetime Achievement Award in 2021, a richly deserved honor for a singular career. She will be missed by all.

The COVID-19 pandemic has profoundly affected society and has caused more than 1 million deaths in the United States and over 6 million deaths worldwide as of the time of this writing. COVID-19 has also affected care in CHD, and a new disease, Multisystem Inflammatory Syndrome in Children, often has cardiac involvement with some patients requiring inotropic and even mechanical support of the circulation. The high number of COVID-19 positive pediatric patients in many parts of the world has led to widespread screening for infection with SARS-CoV2, and alteration of many aspects of anesthetic care, including personal protective equipment and airway protocols. Elective cardiac surgeries at times have been delayed due to overwhelming COVID-19 caseloads straining hospital resources. Education, patient care conferences, and even inpatient and outpatient care have been profoundly affected, with many functions now being conducted over videoconferencing to maintain

social distancing protocols. This Fourth Edition addresses COVID-19 and its effect on CHD care in several chapters: Chapter 8: Multidisciplinary Collaboration, Team Functioning, and Communication in Congenital Cardiac Care; Chapter 18: Preoperative Evaluation and Preparation; Chapter 32: Heart and Lung Transplantation; Chapter 36: Cardiac Intensive Care; and Chapter 37: Mechanical Support of the Circulation. We hope that this new information will be useful to the reader; but our greatest hope is that the COVID-19 pandemic will soon be brought under control through a worldwide effort to heed advice from experts in Medicine, Public Health, Science, and Epidemiology with widespread vaccination and other proven approaches.

Caring for patients with congenital heart disease requires a team of dedicated professionals that include congenital cardiac anesthesiologists, congenital heart surgeons, pediatric and adult congenital cardiologists, cardiac intensivists, cardiac interventionalists and imaging specialists, nurses, perfusionists, respiratory therapists, technicians, child life and social workers, and interpreters, among many others. We greatly appreciate the passion and commitment of the people in these disciplines, without whom we could not do our work. Finally, the patient and family are the focus of the team, and their courage and goodwill in the face of serious and complex illness always amaze and inspire us. It is to our patients and their families that *Anesthesia for Congenital Heart Disease*, Fourth Edition, is also dedicated, in the hope that the knowledge contained in these pages will contribute to better outcomes for them.

It is the purpose of this, our Fourth Edition of *Anesthesia for Congenital Heart Disease*, to contribute to the fund of knowledge in our field, to help prepare the next generation of congenital cardiac anesthesiologists, and to enhance the care of children and adults with congenital heart disease by individuals from various disciplines worldwide.

Dean B. Andropoulos, M.D., M.H.C.M. (Editor-in-Chief)
Emad B. Mossad, M.D.
Erin A. Gottlieb, M.D., M.H.C.M.
June 2022

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List of Abbreviations

α_2M	α_2-macroglobulin
AA	aortic atresia
ABC	Aristotle Basic Complexity
ABO-C	ABO-compatible
ABO-I	ABO-incompatible
ACE	angiotensin-converting enzyme
ACGME	Accreditation Council for Graduate Medical Education
ACHD	adult congenital heart disease
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
AEG	atrial electrogram
AI	aortic insufficiency
AICD	automatic internal cardiac defibrillator
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
Akt	protein kinase B
ALCAPA	anomalous left coronary artery arising from the pulmonary artery
ALI	acute lung injury
ANF	atrial natriuretic factor
ANH	Acute normovolemic hemodilution
APAF-1	apoptotic protease activating factor 1
APERP	accessory pathway effective refractory period
APOE	apolipoprotein E
APRV	airway pressure release ventilation
aPTT	activated partial thromboplastin time
APW	aortopulmonary window
AR	adrenergic receptor
ARCAPA	anomalous right coronary artery from the pulmonary artery
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ASD	atrial septal defect
ASE	American Society of Echocardiography
ASO	arterial switch operation
AT	atrial tachycardia
ATIII	antithrombin III
ATP	adenosine triphosphate
AUC	area under the curve
AV	atrioventricular
AVC	atrioventricular canal
AVNRT	atrioventricular nodal re-entry tachycardia
AVSD	atrioventricular septal defect
BAV	bicuspid aortic valve
Bax	B-cell lymphoma-2-associated X protein
BCAS	The Boston Circulatory Arrest Study
BCL-2	B-cell lymphoma-2
BCL-xL	B-cell lymphoma-extra large
BCPC	bi-directional cavopulmonary connection
BDNF	Brain-derived neurotrophic factor
BiVAD	biventricular ventricular assist device
BNP	brain natriuretic peptide
BOS	bronchiolitis obliterans syndrome
BPA	branch pulmonary artery
BPD	bronchopulmonary dysplasia
BSA	body surface area
BSID	Bayley Scales of Infant Development
BUN	blood urea nitrogen
C3PO	Congenital Cardiac Catheterization Project on Outcomes
CABG	coronary artery bypass grafting
CALM	congenital atresia of the left main coronary artery
cAMP	cyclic adenosine monophosphate
CAV	coronary artery vasculopathy
CAVC	complete atrioventricular canal
CAVF	coronary arteriovenous fistula
CBF	cerebral blood flow
CBG	corticosteroid-binding globulin
CCA	common carotid artery
CCAN	Congenital Cardiac Anesthesia Network
CCAS	Congenital Cardiac Anesthesia Society
CCB	calcium channel blocker
CCTGA	congenitally corrected transposition of the great arteries
CF	cystic fibrosis
cGMP	cyclic guanosine monophosphate
CHARM	Catheterization for Congenital Heart Disease Adjustment for Risk Method
CHD	congenital heart disease
CHF	congestive heart failure
CICU	cardiac intensive care unit
CIED	cardiovascular implantable electronic device
CIRCI	critical illness-related corticosteroid insufficiency
CL	cardiolipin
CLAD	chronic lung allograft dysfunction
CMR	cardiac magnetic resonance
$CMRO_2$	cerebral metabolic rate for oxygen consumption
CMV	cytomegalovirus

CO	carbon monoxide
CO	cardiac output
CoA	coarctation of the aorta
COP	colloid osmotic pressure
COx	cerebral oximetry index
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRBSIs	catheter-related bloodstream infections
CRMDs	cardiac rhythm management devices
CSA	cross-sectional area
CSOR	cerebral–splanchnic oxygen ratio
CT	computed tomography
CUF	conventional ultrafiltration
CVC	central venous catheter
CVVH	continuous veno-venous hemofiltration
CVVH/D	continuous veno-venous hemofiltration and dialysis
DBD	donation after brain death
DCD	donation after cardiac death
DCM	dilated cardiomyopathy
DCRV	double-chambered right ventricle
DHCA	deep hypothermic circulatory arrest
DIC	diffuse intravascular coagulation
DIVA	difficult intravenous access
DLCO	diffusing capacity for carbon monoxide
DLT	double-lumen tube
DNA	deoxyribonucleic acid
DO_2	oxygen delivery
DORV	double outlet right ventricle
D-TGA	dextro-transposition of the great arteries
DVT	deep vein thrombosis
EA	Ebstein's anomaly
EACA	ε-aminocaproic acid
EACTS	European Association for Cardio-Thoracic Surgery
EAT	ectopic atrial tachycardia
EBV	estimated blood volume
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
EDA	end-diastolic area
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction
EFE	endocardial fibroelastosis
EJV	external jugular vein
ELSO	Extracorporeal Life Support Organization
EMA	European Medicines Agency
EMI	electromagnetic interference
EP	electrophysiological
EPDCs	epicardially derived cells
EPO	recombinant human erythropoietin alpha
ERA	endothelin receptor antagonist
ERK	extracellular signal-regulated kinase
ESA	end-systolic area
ESV	end-systolic volume
ET-1	endothelin-1
$EtCO_2$	end-tidal CO_2
ETT	endotracheal tube
FAC	fractional area change
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FHF	first heart field
FiO_2	fraction of inspired oxygen
FOB	fiberoptic bronchoscope
FRC	functional residual capacity
FTR	failure to resuscitate
FV	femoral vein
FVC	forced vital capacity
dATP	deoxyadenosine triphosphate
FVL	Factor V Leiden
GABA	γ-aminobutyric acid
GDP	guanosine diphosphate
GFR	glomerular filtration rate
GI	gastrointestinal
GLUTs	glucose transporters
Gp	glycoprotein
GSK-3β	glycogen synthase kinase-3β
GTP	guanosine triphosphate
HAT	heparin-associated thrombocytopenia
HCII	heparin cofactor II
Hct	hematocrit
HEAL	Health Education Assets Library
HFOV	high-frequency oscillatory ventilation
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLHS	hypoplastic left heart syndrome
HPA	hypothalamic–pituitary–adrenal axis
HPAH	heritable pulmonary artery hypertension
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
HTK	histidine-tryptophan-ketoglutarate
HUS	head ultrasound
IAA	interrupted aortic arch
IABP	intra-arterial blood pressure
IAS	interatrial septum
ICE	intracardiac echocardiography
ICH	intracranial hemorrhage
ICU	intensive care unit
IE	infective endocarditis
IgG	immunoglobulin G
IJV	internal jugular vein
IM	intramuscular
INR	international normalized ratio
iNO	inhaled nitric oxide
IO	inflow occlusion
IPAH	idiopathic pulmonary artery hypertension
IPCCC	International Pediatric and Congenital Cardiac Code
ISHLT	Scientific Registry of the International Society for Heart and Lung Transplantation
IU	international unit
IV	intravenous
IVC	inferior vena cava
IVH	intraventricular hemorrhage

JCAHO	Joint Commission for the Accreditation of Hospital Organizations
JET	junctional ectopic tachycardia
KIM-1	kidney injury molecule-1
LA	left atrium
LAA	left aortic arch
LAA	left atrial appendage
LAP	left atrial pressure
LAS	lung allocation score
LBBB	left bundle branch block
LBW	low birth weight
LBWN	low-birth-weight neonate
LCOS	low cardiac output syndrome
LDLLT	living donor lobar lung transplant
LE	lower esophageal
L-FABP	liver fatty acid-binding protein
LiDCO	lithium dilution CO
LMA	laryngeal mask airway
LMWH	low-molecular-weight heparin
LPA	left pulmonary artery
LQTS	long QT syndrome
LSVC	persistent left superior vena cava
L-TGA	levo-transposition of the great arteries
LV	left ventricle, left ventricular
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MAS	meconium aspiration syndrome
MAT	multifocal atrial tachycardia
mBTS	modified Blalock – Taussig shunt
MCS	mechanical circulatory support
MDI	Mental Development Index
MMF	mycophenolate mofetil
MOD	method of discs
MPA	main pulmonary artery
mPAP	mean pulmonary artery pressure
MPTP	mitochondrial permeability transition pore
MR	mitral regurgitation
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSOF	multisystem organ failure
mTOR	mammalian target of rapamycin
MUF	modified ultrafiltration
MV	mechanical ventilation
NAC	*N*-acetylcysteine
NEC	necrotizing enterocolitis
NGAL	neutrophil gelatinase-associated lipocalin
NICU	neonatal intensive care unit
NIRS	near-infrared spectroscopy
NMDA	*N*-methyl-D-aspartate
NOS	nitric oxide synthase
OB	obliterative bronchitis
OEF	oxygen excess factor
OER	oxygen extraction rate
OHT	orthotopic heart transplantation
OPTN	Organ Procurement and Transplant Network
OR	operating room
$p75^{NTR}$	p75 neurotrophic receptor
PA	pulmonary artery
PA	pulmonary atresia
PA/IVS	pulmonary atresia with intact ventricular septum
PAA	pharyngeal arch arteries
PAC	premature atrial contraction
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PAD	preoperative autologous donation
PAH	pulmonary arterial hypertension
PAH-CHD	pulmonary arterial hypertension associated with congenital heart disease
PAI	plasminogen activator inhibitor
PAO_2	alveolar oxygen tension
PaO_2	partial pressure of oxygen in arterial blood
PAPVC	partial anomalous pulmonary venous connection
PAPVD	partial anomalous pulmonary venous drainage
PAPVR	partial anomalous pulmonary venous return
PASP	pulmonary artery systolic pressure
PBF	pulmonary blood flow
PC	protein C
pCAS	pediatric cardiopulmonary assist system
PCC	prothrombin complex concentrate
PCWP	pulmonary capillary wedge pressure
PD	peritoneal dialysis
PDA	patent ductus arteriosus
PDC	peritoneal drainage catheter
PDE	phosphodiesterase
PDE-5	phosphodiesterase-5
PDEIs	phosphodiesterase inhibitors
PEEP	positive end-expiratory pressure
PEO	proepicardial organ
PF4	platelet factor 4
PFO	patent foramen ovale
PG	pressure gradient
PGE_1	prostaglandin E_1
PH	pulmonary hypertension
PHT	pulmonary hypertension
PI	pulmonary insufficiency
PICC	peripherally inserted central catheter
PIP	peak inspiratory measurement
PI-PLC	phosphatidylinositol-specific phospholipase C
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PMP	poly-(4-methyl-1-pentene)
POCA	Pediatric Perioperative Cardiac Arrest Registry
PPL	polypropylene
PPS	postpericardiotomy syndrome
PPV	positive pressure ventilation
PRA	panel reactive antibody
pRIFLE	pediatric modification of the RIFLE (**Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease**) score
PRISM	Pediatric Risk of Mortality
PS	protein S
PS	pulmonary stenosis

PS/IVS	pulmonary stenosis with intact ventricular septum
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PTT	partial thromboplastin time
PV	pulmonary valve
PVCs	premature ventricular contractions
PVD	pulmonary vascular disease
PVP	pulmonary valve perforation
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
Qp	pulmonary blood flow
Qs	systemic blood flow
RA	right atrium
RAA	right aortic arch
RACHS-1	Risk Adjustment for Congenital Heart Surgery 1
RAP	right atrial pressure
RBBB	right bundle branch block
RBC	red blood cell
RCP	regional cerebral perfusion
RDS	respiratory distress syndrome
rFVIIa	recombinant activated factor VIIa
RIFLE	risk, injury, failure, loss, and end-stage renal disease
RIPC	remote ischemic preconditioning
ROS	reactive oxygen species
RPA	right pulmonary artery
RV	right ventricle, right ventricular
RVDCC	right ventricle-dependent coronary circulation
RVOT	right ventricular outflow tract
RVOTO	right ventricular outflow tract obstruction
RVSP	right ventricular systolic pressure
SAN	sinoatrial node
SaO_2	arterial oxygen saturation
SCA	Society of Cardiovascular Anesthesiologists
SCPA	superior cavopulmonary anastomosis
SCV	subclavian vein
$ScvO_2$	central venous oxygen saturation
SERCA	sarcoplasmic reticulum Ca^{2+}-ATPase
SF	shortening fraction
SGOT	serum glutamic oxaloacetic transaminase
SHF	second heart field
SIRS	systemic inflammatory response syndrome
$SjvO_2$	jugular bulb venous oximetry
SLV	single-lung ventilation
SPA	Society for Pediatric Anesthesia
SpO_2	pulse oximeter saturation
SR	sarcoplasmic reticulum
SSI	surgical site infection
STAT	Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery mortality score
STS	Society of Thoracic Surgeons
STS-CHSD	Society of Thoracic Surgeons Congenital Heart Surgery Database
subAS	subvalvular aortic stenosis
SV	stroke volume
SVAS	congenital supravalvular aortic stenosis
SVC	superior vena cava
SvO_2	percentage of oxygen saturation of mixed venous blood
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
SVT	supraventricular tachycardia
T3	triiodothyronine
T4	thyroxine
TA	tranexamic acid
TA	tricuspid atresia
TAFI	thrombin-activatable fibrinolysis inhibitor
TAPVC	total anomalous pulmonary venous connection
TAPVR	total anomalous pulmonary venous return
TCAD	transplant coronary artery disease
TDI	tissue Doppler imaging
TEE	transesophageal echocardiography
TEG	thromboelastography
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGA	transposition of the great arteries
TGC	tight glycemic control
TI	tricuspid valve (TV) insufficiency
TLC	total lung capacity
TNF-alpha	tumor necrosis factor-alpha
TOF	tetralogy of Fallot
TOR	target of rapamycin protein
tPA	tissue plasminogen activator
TPTD	transpulmonary thermodilution
TR	tricuspid regurgitation
TRALI	transfusion-related acute lung injury
TTE	transthoracic echocardiography
TV	tricuspid valve
UFH	unfractionated heparin
UNOS	United Network for Organ Sharing
URI	upper respiratory tract infection
V/Q	ventilation/perfusion
VA	ventriculoarterial
VAA	volatile anesthetic agent
VAC	video-assisted cardioscopy
VAD	ventricular assist device
VATS	video-assisted thoracoscopic surgery
VF	ventricular fibrillation
VMI	visual-motor integration
VO_2	oxygen consumption
vPEO	venous proepicardial organ
VSD	ventricular septal defect
VT	ventricular tachycardia
VTI	velocity time integral
vWF	von Willebrand factor
WHO	World Health Organization
WMI	white matter injury
WS	Williams syndrome
WUS	Wake Up Safe Database

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About the Companion Website

Anesthesia for Congenital Heart Disease: Companion Website

Additional resources to accompany this book are available at:

www.wiley.com/go/andropoulos/congenitalheart



Included on the site:

Full reference lists

CHAPTER 1

History of Anesthesia for Congenital Heart Disease

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Introduction

Over the last 80+ years, congenital cardiac anesthesia has developed as a subspecialty of pediatric and/or cardiac anesthesia, depending on one's perspective. It is impossible to describe the evolution of congenital cardiac anesthesia without simultaneously referring to developments in the surgical and interventional management of congenital heart disease (CHD) due to the great interdependency of these fields. As pediatric anesthesia developed, surgical treatments and percutaneous interventions for children with CHD began to be devised, starting with the simple surgical ligation of a patent ductus arteriosus (PDA). Over the years, the continual development and refinement of surgical and interventional techniques has led to the introduction of staged palliations, increasingly sophisticated repairs of complex intracardiac lesions requiring cardiopulmonary bypass (CPB) and circulatory arrest, and most recently, of complex biventricular repairs. These advances were accompanied by concurrent changes in anesthetic management that overcame the technical challenges and mitigated the perioperative morbidity associated with these novel techniques.

This chapter will be organized primarily around the theme of how anesthesiologists met these new challenges using the anesthetic armamentarium that was available to them at the time. The secondary theme running through this history is the gradual shift from a purely intraoperative focus to one with a view of the entirety of the perioperative period. Not surprisingly, the drastic decreases in surgical mortality have led to an increased interest in the reduction of perioperative morbidity. The final theme is the progressive and ongoing expansion in the age range of patients routinely presenting for congenital cardiac surgery.

The first years: 1938–1954

The first successful operation for CHD was performed in August 1938 when Robert E. Gross ligated the PDA of a 9-year-old girl. The operation and the postoperative course were smooth, but because of the interest in the case, the child was kept in the hospital until the 13th postoperative day. In the report of the case, Gross mentions that the operation was done under cyclopropane anesthesia, and continues: "The chest was closed, the lung being re-expanded with positive pressure anesthesia just prior to placing the last stitch in the intercostal muscles." A nurse using a "tight-fitting" mask delivered the anesthetic. There was no intubation and, of course, no postoperative ventilation. The paper does not mention any particular pulmonary complications, so it cannot have been much different from the ordinary postoperative course of the day [1].

In 1952, Dr. Gross published a review of 525 PDA ligations where many, if not all, of the anesthetics were administered by the same nurse anesthetist, under surgical direction [2]. Here he states: "Formerly, we employed cyclopropane anesthesia for these cases, but since about half of the fatalities seemed to have been attributable to cardiac arrest or irregularities under this anesthetic, we have now completely abandoned cyclopropane and employ ether and oxygen as a routine." It is probably correct that cyclopropane under these circumstances with insufficient airway control was more

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likely than ether to cause cardiac arrhythmias. An intralaryngeal airway was used, which also served "to facilitate suction removal of any secretions from the lower airway" (and, we may add, the stomach). Dr. Gross claims that the use of this airway reduced the incidence of postoperative pulmonary complications. Without a modern, rigorous review of this series, it is hard to know what other particular anesthetic challenges were confronted by the anesthetists, but we may assume that intraoperative desaturation from the collapsed left lung, postoperative pulmonary complications, and occasional major blood loss from an uncontrolled, ruptured ductus arteriosus were high on the list.

The next operation to be introduced, the systemic to pulmonary artery (PA) shunt, was billed as "corrective" for the child with cyanotic CHD. The procedure was proposed by Helen Taussig as an "artificial ductus arteriosus" and was first performed by Albert Blalock and the surgical technician Vivien Thomas at the Johns Hopkins Hospital in 1944. In a very detailed paper, Drs. Blalock and Taussig described the first three patients to undergo the Blalock–Taussig shunt operation, recently recognized as Blalock-Thomas-Taussig shunt. Dr. Harmel anesthetized the first and third patients, using ether and oxygen in an open drop method for the former and cyclopropane through an endotracheal tube for the latter. The second patient was given cyclopropane through an endotracheal tube by Dr. Lamont. Whether the first patient was intubated is unclear, but it is noted that in all three cases, positive pressure ventilation was used to reinflate the lung [3]. Interestingly, in this early kinder and gentler time, the surgical and pediatric authors reporting the Blalock–Taussig operation acknowledged by name the pediatricians and house officers who took such good care of the children postoperatively, but still did not acknowledge the contribution of the anesthesiologists, Lamont and Harmel. Although intubation of infants was described by Gillespie as early as 1939, it is difficult to say precisely when intubations became routine [4].

Drs. Harmel and Lamont reported in 1946 on their anesthetic experience of 100 operations for congenital malformations of the heart "in which there is pulmonary artery stenosis or atresia." They reported 10 anesthetic-related deaths in the series, so it is certain that they encountered formidable anesthetic problems during these surgical procedures [5]. In 1952, Damman and Muller reported a successful operation in which the main PA was reduced in size and a band was placed around the artery in a 6-month-old infant with a single ventricle (SV). They state that morphine and atropine were given preoperatively, but no further anesthetic agents are mentioned. At that time, infants were assumed to be oblivious to pain, so we can only speculate on what was used beyond oxygen and restraint [6].

Over the next 20 years, many palliative operations for CHD were developed and a number of papers describing the procedures and their anesthetic management appeared in the literature. In 1948, McQuiston described the anesthetic technique used at the Children's Memorial Hospital in Chicago [7]. This is an excellent paper for its time, however, a number of the author's conclusions are erroneous. The anesthetic technique for shunt operations (mostly Potts' anastomosis) is discussed in some detail but is mostly of historical interest today. McQuiston explained that he had no experience of anesthetic management used in other centers, such as the pentothal–N_2O–curare used at Minnesota or the ether technique used at the Mayo Clinic. McQuiston used heavy premedication with morphine, pentobarbital and atropine, and/or scopolamine; this is emphasized because it was important "to render the child sleepy and not anxious." The effect of sedation with regard to a decrease in cyanosis (resulting in making the child look pinker) is noted by the authors. They also noted that children with severe pulmonic stenosis or atresia do not decrease their cyanosis "because of very little blood flow," and that these children have the highest mortality. McQuiston pointed out that body temperature control was an important factor in predicting mortality and advocated the use of moderate hypothermia (i.e., "refrigeration" with ice bags), because of a frequently seen syndrome of hyperthermia. McQuiston worked from the assumption that hyperthermia is a disease in itself, but did not explore the idea that the rise in central temperature might be a symptom of low cardiac output with peripheral vasoconstriction. Given what we now know about shunt physiology, it is interesting to speculate that this "disease" was caused by pulmonary hyperperfusion after the opening of what would now be considered as an excessively large shunt, stealing a large portion of systemic blood flow.

In 1950, Harris described the anesthetic technique used at Mount Zion Hospital in San Francisco [8]. He emphasized the use of heavy premedication with morphine, atropine, and scopolamine. The "basal anesthetic agent" was Avertin (tribromoethanol) administered rectally and supplemented with N_2O/O_2 and very low doses of curare. Intubation was facilitated by cyclopropane with FiO_2 titrated according to cyanosis throughout. Bucking or attempts at respiration were thought to be due to stimulation of the hilus of the lung and were treated with "cocainization" of the hilus [8].

In 1952, Dr. Robert M. Smith discussed the circulatory factors involved in the anesthetic management of patients with CHD [9]. The anesthetic agents recommended were mostly ether following premedication. He pointed out the necessity of understanding the pathophysiology of the lesion and also "the expected effect of the operation upon this unnatural physiology." That is, he recognized that the operations were not curative. While most of the previous papers had been about tetralogy of Fallot (TOF), Dr. Smith also described the anesthetic challenges of surgery for coarctation of the aorta, introduced simultaneously in 1945 by Dr. Gross in the United States and Dr. Craaford in Sweden. He emphasized hypertension following clamping of the aorta and warned against excessive bleeding in children operated on at older ages using ganglionic blocking agents. This bleeding was far beyond what anesthesiologists now see in patients operated on at younger ages, before the development of substantial collateral arterial vessels [9].

The heart–lung machine: 1954–1970

From 1954 to 1970 the development of what was then called the "heart–lung machine" allowed for the surgical repair of complex intracardiac congenital heart defects.

Early CPB technology was associated with significant morbidity and mortality, especially in smaller children weighing less than 10 kg. In Kirklin's initial report of intracardiac surgery utilizing a mechanical pump–oxygenator system at the Mayo Clinic, the only reference to anesthetic management was a brief remark that ether and oxygen were given [10]. In Lillehei's description of direct vision intracardiac surgery in humans using a simple, disposable artificial oxygenator, there was no mention of anesthetic management [11]. What strikes a "modern" cardiac anesthesiologist in these two reports is the high mortality: 50% in Kirklin's series and 14% in Lillehei's series. All of these patients were children with CHD ranging in age from 1 month to 11 years.

Anesthetic challenges multiplied rapidly with the introduction of CPB and early attempts at intracardiac repairs. At that time, most anesthetics were performed by nurses under the supervision of the surgeon utilizing ether (first with open drop ether administration and later using various non-rebreathing systems) or cyclopropane. In most early textbooks, cyclopropane was the recommended drug for pediatric anesthesia despite the fact that it was both explosive and difficult to use. CO_2 absorption was necessary with cyclopropane in order to avoid hypercarbia and acidosis, which might precipitate ventricular arrhythmias. The use of a Waters' absorber, however, could be technically difficult, especially as tracheal intubation was considered to be dangerous to the child's "small, delicate airway."

In all of the early reports, it is noted or implied that the patients were awake (more or less) and extubated at the end of the operation. In the description of the postoperative course, respiratory complications were frequent, in the form of either respiratory insufficiency or airway obstruction. The former problem was likely related to the morbidity of early bypass technology on the lung, while the latter problem was probably because "the largest tube which would fit through the larynx" was often used and/or that the red rubber tube was not tissue tested.

Arthur S. Keats, who worked with Denton A Cooley at the Texas Heart Institute and Texas Children's Hospital starting in 1955, had significant experience with congenital heart surgery and anesthesia and provided the most extensive description of the anesthetic techniques used in this era. He described anesthesia for congenital heart surgery without bypass in 150 patients, the most common operations being PDA ligation, Potts' operation, atrial septectomy (Blalock–Hanlon operation), and pulmonary valvotomy [12]. Patients were administered a generous premedication of pentobarbital or chloral hydrate along with meperidine or atropine. Endotracheal intubation was utilized, and ventilation was assisted using an Ayres T-piece, to-and-fro absorption system, or a circle system. Cyclopropane was used for induction, and a venous cutdown provided vascular access. A succinylcholine bolus and infusion were used to maintain muscle relaxation. Light ether anesthesia was used for maintenance until the start of chest closure, at which point 50% N_2O was used as needed. Electrocardiogram (ECG), ear oximeter, and intra-arterial blood pressure (IABP) recordings were used for monitoring during this period, as were arterial blood gases and measurements of electrolytes and hemoglobin. The following year, he published his experiences with 200 patients undergoing surgery for CHD with CPB, almost all of whom were children [13]. Ventricular septal defect (VSD), atrial septal defect (ASD), TOF, and aortic stenosis were the most common indications for surgery. The anesthetic techniques were the same as described earlier, except that D-tubocurare was given to maintain apnea during the bypass.

Perfusion rates of 40–50 mL/kg/min were used in infants and children, and lactic acidemia after bypass (average 4 mmol/L) was described. No anesthetic agent was added during the bypass procedure, and "patients tended to awaken during the period of bypass," but apparently without recall or awareness. Arrhythmias noted ranged from frequent bradycardia with cyclopropane and succinylcholine to junctional or ventricular tachycardia, ventricular fibrillation (VF), heart block, and rapid atrial arrhythmias. Treatments included defibrillation, procainamide, digitalis, phenylephrine, ephedrine, isoproterenol, and atropine. Eleven out of 102 patients with VSD experienced atrioventricular block. Epicardial pacing was attempted in some of these patients but was never successful. Fresh citrated whole blood was used for small children throughout the case, and the transfusion of large amounts of blood was frequently necessary in small infants. The mortality rate was 13% in the first series (36% in the 42 patients less than 1-year-old) and 22.5% in the second series (47.5% in the 40 patients less than 1-year-old). Causes of death included low cardiac output after ventriculotomy, irreversible VF, coronary air emboli, postoperative atrioventricular block, hemorrhage, pulmonary hypertension, diffuse atelectasis, and aspiration of vomitus. No death was attributed to the anesthetic alone. Reading these reports provides an appreciation of the daunting task of providing anesthesia during these pioneering times. In 1957, in addition to ECG, IABP, and oximeter, Dr. Digby Leigh noted the importance of capnography in cardiac surgery. He described the effect of pulmonary blood flow on end-tidal CO_2 ($EtCO_2$) and the decrease in $EtCO_2$ after partial clamping of the PA during the Blalock–Taussig shunt procedure. However, it was not until 1995 that Smolinsky et al. reported the importance of $EtCO_2$ during PA banding [14–16].

Tracheostomy after cardiac operations was not unusual, and in some centers, it was done "prophylactically" a week before the scheduled operation. These practices were certainly related to primitive (relative to the present) techniques and equipment used for both endotracheal intubation and CPB. Postoperative ventilatory support did not become routine until later when neonatologists and other intensive care specialists had proven that it could be done successfully. Successful management of prolonged respiratory support was first demonstrated in the great poliomyelitis epidemics in Europe and the United States in 1952–1954 [17].

Halothane was introduced into clinical practice in the mid-1950s and rapidly became the most popular agent in pediatric anesthesia as it allowed for a smoother induction. Halothane was also widely used for pediatric cardiac

anesthesia despite its depressive effect on the myocardium and its significant risk of arrhythmia. During this period, adult cardiac anesthesiologists, following the practice reported by Edward Lowenstein in 1970 [18], began to use opiate-based intravenous anesthesia. Initially, morphine in doses up to 1 mg/kg was given with 100% oxygen and this technique became the anesthetic of choice for adult cardiac patients, but vasodilation and hypotension associated with its use slowed the incorporation of this technique in pediatric cardiac anesthesia until synthetic opiates became available.

Both prior to the development of CPB and during its early implementation, a number of modalities were utilized to improve outcomes in infants. Inflow occlusion (IO) was an elegant technique that required close cooperation between the entire operating room team, but most especially between the surgeon and the anesthesiologist. The technique was as follows: The chest was opened in the midline. After pericardiotomy, a side clamp was placed on the right atrial (RA) free wall and an incision made in the RA, or proximal on the PA, prior to placing the vascular clamps used to occlude caval return. Before application of the clamps, patients were hyperventilated with 100% O_2. During IO, the superior vena cava (SVC) and inferior vena cava (IVC) inflow were occluded, ventilation held, and the RA or PA clamp released. The heart was allowed to empty and the septum primum was excised or the pulmonic valve dilated. After excision of the septum or valvotomy, one caval clamp was released to de-air the atrium. The RA side clamp or the PA clamp was then reapplied and the other caval clamp was released. The heart was resuscitated with bolus calcium gluconate (range 30–150 mg/kg) and bicarbonate (range 0.3–3 mEq/kg). Occasionally, inotropes were administered, most often dopamine. It was important to titrate the inotropes so as not to aggravate rebound hypertension caused by endogenous catecholamines. The duration of the IO was between 1 and 3 minutes – terrifying minutes for the anesthesiologist, but quickly over.

Another modality used to try to improve the survival after shunt operations, PA banding, and atrial septectomy was to operate in the hyperbaric chamber, thereby benefiting from the increased amount of physically dissolved oxygen [19] (Figure 1.1). It was a cumbersome affair operating in crowded, closed quarters. There was only room for two surgeons, two nurses, one anesthesiologist, and one baby, as the number of emergency oxygen units limited access. Retired navy divers ran the chamber and kept track of how many minutes the personnel had been in the hyperbaric chamber in the previous week. Help was not readily available because the chamber was buried in a sub-basement and people had to be sluiced in through a side arm that could be pressurized. The chamber was pressurized to 2–3 atmospheres so it was unpleasantly hot while increasing the O_2 pressure and cold while decreasing the pressure. People with glasses were at a disadvantage. Providing anesthesia was also a challenge. Infants were anesthetized with ketamine and nitrous oxide. As the pressure in the chamber increased, the concentrations of N_2O had to be decreased to avoid hypotension and bradycardia. The hyperbaric chamber did not seem to improve survival and was abandoned around 1974.

It was also during this era that the first infant cardiac transplant was performed by Kantrowitz in 1967 [20]. The recipient was an 18-day-old, 2.6 kg patient with severe Ebstein's anomaly, who had undergone a Potts' shunt on day 3 of life. The donor was an anencephalic newborn. The anesthetic technique is not described, and the infant died of pulmonary dysfunction 7 hours postoperatively.



Figure 1.1 Hyperbaric chamber at Boston Children's Hospital in 1972. (Source: Odegard and Rockoff [19]. Reproduced with permission from John Wiley & Sons.)

AL Grawany

Deep hypothermic circulatory arrest and the introduction of PGE_1: 1970–1980

Sometime around 1970, the physiological repair of CHD, or "correction," began to come of age. Children were still treated as "small adults" because major physiological differences were not yet well appreciated, particularly as related to CPB morbidity. CPB was rarely employed during surgery on pediatric patients weighing less than 9 kg due to the very high morbidity and mortality experienced during the early years. The notion of repairing complex CHD in infancy was gaining attention but was hindered by the limitations of surgical, CPB and anesthetic techniques in infants. Theoretically, physiological repair early in life provides a more normal development of the cardiovascular and pulmonary systems and may altogether avoid palliative procedures and their adverse sequelae (e.g. anatomic distortions secondary to shunt and/or banding procedures and/or PA hypertension secondary to pulmonary vascular occlusive disease following Waterston and Potts' shunts). Furthermore, parents could be spared the anxiety of repeated operations and the difficulties of raising a child with a partially palliated heart and abnormal physiology.

The perceived need for early repair, together with the high mortality of CPB procedures in infants and small children, led to the introduction of deep hypothermic circulatory arrest (DHCA). First practiced in Kyoto, Japan, the use of DHCA then spread to pediatric centers in Russia and the United States. The first description of DHCA in the English surgical literature was published by Horiuchi in 1963 [21]. This involved a simple technique of surface cooling and rewarming during resuscitation, using ether as the anesthetic agent without intubation. In 1972, Mori et al. reported details of a technique for cardiac surgery in neonates and infants using deep hypothermia [22]. The infants were surface-cooled with ice bags and rewarmed on CPB. The anesthetic was maintained with halothane/N_2O combined with muscle relaxant and CO_2 was added to the anesthetic gas during cooling and rewarming (pH-stat) in order to improve cerebral perfusion. Another paper from Toronto described an anesthetic regime with atropine premedication occasionally combined with morphine [23]. Halothane and 50% N_2O were used, combined with D-tubocurarine or pancuronium. CO_2 was added to "improve tissue oxygenation by maintaining peripheral and cerebral perfusion." The infants were cooled with surface cooling (plastic bags with melting ice) and rewarmed on CPB. It was noted that 6 of the 25 infants had VF when cooled below 30 °C.

Surprisingly, given the enormity of the physiological disturbances and challenges presented by DHCA, very few articles describing an anesthetic technique for DHCA were published in the anesthesia literature, perhaps because DHCA and early surgical repair were not widely accepted. The material that was published about these techniques was restricted to surgical journals and was largely unknown to cardiac and pediatric anesthesiologists. Given the lack of scientific data to guide the anesthetic management of such cases, a very simple technique with ketamine–O_2–N_2O and curare supplemented by small amounts of morphine (0.1–0.3 mg/kg) was used at Boston Children's Hospital. Palliative cardiac surgical procedures were performed in the hyperbaric chamber. The infants were surface-cooled in a bathtub filled with ice water to a core temperature of approximately 30 °C. The bathtub consisted of a green plastic bucket (for dishwashing) bought at a Sears-Roebuck surplus store, keeping things as simple as possible [19] (Figure 1.2). This method was used in hundreds of infants over the next couple of years and only one infant developed VF, secondary to a coronary air embolus either from a peripheral IV or during an attempted placement of a central venous line, rather than the cooling itself (Figure 1.3).

During the first year of using DHCA in Boston, it was noticed that a number of the infants had "funny, jerky" movements of the face and tongue. A few also had transient

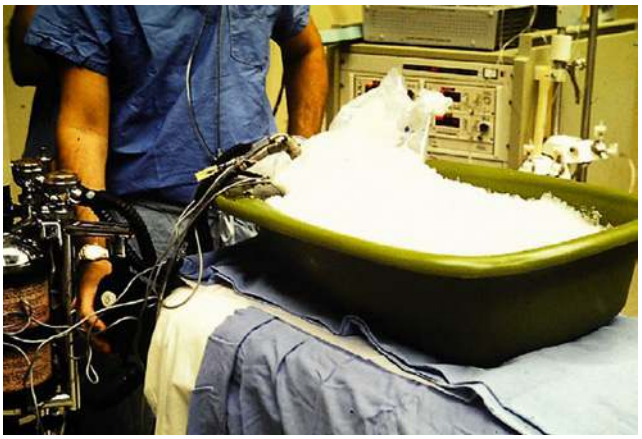


Figure 1.2 A neonate with hypoplastic left heart syndrome submerged in ice before surgery. (Source: Odegard and Rockoff [19]. Reproduced with permission from John Wiley & Sons.)



Figure 1.3 A neonate with hypoplastic left heart syndrome ready for surgery after being cooled in ice. (Source: Odegard and Rockoff [19]. Reproduced with permission from John Wiley & Sons.)

seizures during the postoperative period, but as they had normal electroencephalograms (EEGs) at 1-year follow-up, it was felt that significant cerebral complications were not a problem. In view of the knowledge developed subsequently, these clues to neurological damage occurring during and after pediatric cardiac surgery involving DHCA were overlooked. In hindsight, it is perhaps more accurate to say that these clues were ignored, and as a result, a great opportunity to study this problem was delayed for almost two decades. The issue of neurological damage with DHCA was raised repeatedly by surgeons such as John Kirklin, but was not intensively studied until the group at Boston Children's Hospital led by Jane Newburger and Richard Jonas systematically followed a cohort of infants who had undergone the arterial switch operation in the late 1980s using DHCA techniques [24]. In the late 1980s and early 1990s, Greeley et al. at Duke performed a series of human studies delineating the neurophysiological response to deep hypothermia and circulatory arrest [25]. These studies provided crucial data from which strategies for cooling and rewarming, length of safe DHCA, blood gas management (pH-stat versus alpha-stat during hypothermic CPB), and perfusion (DHCA with hypothermic low-flow perfusion, hematocrit in the perfusate) were devised in order to maximize cerebral protection.

From the beginning of this period, surgical results as measured by mortality alone were excellent, with steady increases in raw survival statistics. Because anesthetic techniques were evolving over this period of time, it was difficult to definitively ascribe any outcome differences to different anesthetic agents. A 1984 study of 500 consecutive cases of cardiac surgery in infants and children looked at anesthetic mortality and morbidity. Both were very low – so low in fact that they were probably not universally believed [26].

As new synthetic opioids such as fentanyl and sufentanil were developed, they replaced morphine to provide more hemodynamic stability in opiate-based anesthetic techniques for cardiac patients. This technique slowly and somewhat reluctantly made its way into pediatric anesthesia [27], replacing halothane, ketamine, and morphine, which had previously been the predominant choice of pediatric anesthesiologists dealing with patients with CHD. In 1981, Gregory et al. first described the use of "high-dose" fentanyl 30–50 μg/kg combined with pancuronium in 10 infants undergoing PDA ligation [28]. It is noteworthy that transcutaneous oxygen tension was measured as part of this study. This paper was, in fact, the introduction of high-dose narcotics in pediatric cardiac anesthesia [28]. The technique was a great success. One potential reason for this was determined several years later by Anand et. al. who demonstrated that fentanyl attenuated the stress response in infants undergoing PDA ligation [29].

In the years from 1983 to 1995, a number of papers were published showing the effect of different anesthetic agents on the cardiovascular system in children with CHD. Ketamine, nitrous oxide, fentanyl, and sufentanil were systematically studied. Some misconceptions stemming from studies of adult patients were corrected, such as the notion that N_2O combined with ketamine raises PA pressure and pulmonary vascular resistance (PVR) [30]. On the other hand, increased $PaCO_2$ and lower pH were shown to cause higher PVR immediately postoperatively [31]. A number of studies done at this time demonstrated (in a controlled fashion) the earlier clinical observation by Harmel and McQuiston in the late 1940s. [5, 32] that in cyanotic patients the O_2 saturation would rise during the induction of anesthesia, almost irrespective of the agent used [33]. These events only serve to reinforce the value of acute clinical observation and provide an example of how the interpretation of such observations may well change as new knowledge is discovered.

It was also during this decade that the "team concept" developed at larger centers, with cardiologists, cardiac surgeons, and anesthesiologists working closely together in the OR and the intensive care unit (ICU). These teams were facilitated by the anesthesiologists' "invasion" of weekly cardiology/cardiac surgery conferences where the scheduled operations for the week were discussed. Dr. Castaneda, the chief surgeon at Boston Children's Hospital, was a leader in the creation of the cardiac team concept for pediatric cardiac surgery.

PDA and the introduction of PGE_1

The medical and surgical management of PDA presents an interesting story. In 1938, Dr. Robert Gross became the first to successfully correct a CHD lesion when he surgically ligated a PDA in a 9-year-old girl. [1]. Fifty years later, it would also be the first CHD lesion to be corrected in the catheterization laboratory [34]. In the intervening years, several discoveries were made that turned out to be of great clinical significance to the pediatric cardiac anesthesiologist and the entirety of the cardiac team. During this time, pharmacological treatment of PDA was developed, and perhaps more importantly, it was discovered that the intravenous infusion of PGE_1 prevented the closure of the ductus arteriosus [35]. As the critical role of the ductus arteriosus in the pathophysiology and management of cyanotic and acyanotic CHD was increasingly appreciated, clinicians sought methods of maintaining ductal patency or achieving ductal closure, depending on the type of CHD encountered.

As neonatal intensive care advanced and the understanding of the physiology of this patient population expanded, the survival rates of very small and increasingly premature infants improved. It became apparent that in many of these infants, the ductus arteriosus would remain patent rather than undergo normal closure and that this continued patency had a deleterious effect on mechanical ventilation. In the 1970s, this appreciation led to the institution of medical therapy using aspirin (and later indomethacin, ibuprofen, and acetaminophen) in order to promote ducal closure. When such pharmacologic attempts at closure failed, it was increasingly understood that necrotizing enterocolitis (NEC) in the premature neonate was associated with decreased mesenteric blood flow secondary to the "steal" of systemic blood flow into the

pulmonary circulation through a PDA. Thus, in cases when the PDA failed to close in premature infants, the need for operative treatment of the PDA arose as prophylaxis for necrotizing enterocolitis.

Pediatric and cardiac anesthesiologists were then faced with the task of anesthetizing these tiny patients safely. As the decade progressed, issues such as temperature, maintenance fluid, and the prevention of secondary injury arose and were addressed emerged and were addressed. In 1980, Neuman described the anesthetic management of 70 such infants using an O_2/N_2O muscle relaxant anesthesia technique with no mortality [36]. Low FiO_2 was used to reduce the risk of retrolental fibroplasia and precautions were taken to prevent heat loss. In those days, 40% of the infants received a blood transfusion. Interestingly, the question of whether to operate in the neonatal intensive care unit (NICU) or the OR for closure of the PDA was debated at that time and remains unsettled even today.

Presently, if surgical closure is necessary, it is often done using a minimally invasive, thoracoscopic video-assisted technique [37]. Thoracoscopy has the benefit of using four tiny incisions to insert the instruments, avoiding an open thoracotomy, and limiting dissection and trauma to the left lung. At the same time, this latest development of surgical techniques required the anesthesiologist once again to change the anesthetic approach to these patients. Unlike adult anesthesiologists, who can use double-lumen endotracheal tubes for thoracoscopic procedures, pediatric anesthesiologists caring for 1–3 kg infants undergoing PDA ligation do not have the luxury of managing the left lung [37]. Another problem posed by thoracoscopic PDA ligation in the infant is the emerging need for neurophysiological monitoring of the recurrent laryngeal nerve's innervation of the muscles of the larynx to avoid injury, a known complication of PDA surgery [38]. The last issue is tailoring the anesthetic so that the children are awake at the end of the operation, extubated, and spend an hour or so in the post-anesthesia care unit, bypassing the cardiac ICU. In fact, in 2001, a group led by Hammer at Stanford published the first description of true outpatient PDA ligation in two infants aged 17 days and 8 months [39]. These patients were managed with epidural analgesia, extubated in the OR, and discharged home 10 hours postoperatively. This report brings PDA closure full circle from a 13-day hospital stay following an ether mask anesthetic for an open thoracotomy to a day surgery procedure in an infant undergoing an endotracheal anesthetic for a thoracoscopic PDA ligation.

Maintaining the patency of the PDA using PGE_1 is probably now of considerably greater importance than its closure. The introduction of PGE_1 suddenly improved the survival rate of a large number of neonates with ductal-dependent CHD. It also drastically changed the clinical practice of pediatric cardiac surgeons and anesthesiologists as frequent, middle-of-the-night shunt operations with extremely cyanotic infants almost immediately became a thing of the past. These operations were particularly daunting when one realizes that these procedures were most commonly performed before the availability of pulse oximetry – the only warning signs of impending cardiovascular collapse were the very dark color of the blood and preterminal bradycardia. To get an arterial blood gas with a PaO_2 in the low teens was not uncommon and PaO_2 measurements in single digits in arterial blood samples from live neonates during such surgical procedures were reported. PGE_1 also dramatically improved the care of the neonate with critical post-ductal coarctation. Prior to PGE1, these infants were extremely acidotic, with a pH of 7.0 or less at the start of the procedure (if it was possible to obtain an arterial puncture); they looked mottled and almost dead below the nipples. With the advent of PGE_1 therapy, they were resuscitated medically in the ICU and could be operated on the following day in substantially better condition than was previously the case.

But the introduction of PGE_1 had an effect that was not clearly foreseen except possibly by few astute cardiologists. An increasing number of neonates with severe forms of CHD that had hitherto been considered a "rare" pathological diagnosis were now surviving and presenting for care. Foremost among these were the infants with hypoplastic left heart syndrome (HLHS) and some forms of the interrupted aortic arch. As further experience was gained, it became obvious that these forms of the disease were not so rare, but that infants who had survived with those forms of CHD were.

The story of HLHS: 1980–1990

As mentioned in the previous section, the introduction of PGE_1 brought major changes to the practice of pediatric cardiac anesthesia, solving some problems but at the same time, introducing new challenges. New diagnoses of CHD were recognized and presented for treatment while, as did some that had previously been known but until then had presented insurmountable obstacles to effective therapy. One of these latter types of lesions was HLHS.

HLHS had been accurately described in 1958 by Noonan and Nadas, but only as a pathological diagnosis [40]. In the beginning, most of the infants were misdiagnosed as having sepsis, and few babies reached a tertiary center without a telltale Band-Aid®, indicating a lumbar puncture. HLHS is a ductal-dependent lesion, with 100% mortality within a few days to weeks as the ductus undergoes physiological closure. HLHS was therefore of no practical interest from a therapeutic standpoint until ductal patency could be maintained. When this became possible with PGE_1, these neonates rapidly became a problem that could not easily be ignored. Even with the ability to diagnose the defect in a live neonate temporarily kept alive with a PGE_1 infusion, the outlook was not much better as there was no palliative operation yet devised. In some centers, such neonates were kept viable on a PGE_1 infusion for weeks or even months in the (usually) vain attempt to get them to grow large enough for a surgical procedure to be attempted. Those were also the years during which President Ronald Reagan's Baby Doe regulations were in effect. Anyone who thought an infant was being mistreated (i.e. not operated upon) could call a "hotline number" that was posted in all neonatal ICUs to report the physicians' "mistreatment" of the infant. Fortunately, these regulations died a quiet death after a few chaotic years [41].

In subsequent years, several centers tried different approaches with ingenious conduits, attempting to create an outlet from the right ventricle to the aorta and the systemic circulation. The search for a palliative operation was spurred by the increasing success of the Fontan operation, which had been introduced in 1970 [42]. This meant that there now was a theoretical endpoint for HLHS as well as for other forms of the SV physiology. It was William Norwood at Boston Children's Hospital who was the first person to devise a viable palliation and also to complete the repair with a Fontan operation the following year [43]. The publication of this landmark paper spurred considerable discussion. Many cardiologists and surgeons took the position that this operative procedure represented experimental and unethical surgery and that these infants "were better off dead."

The current approach to these infants varies somewhat by center, but is most commonly a multistage palliation culminating with a Fontan operation. Another, albeit historical at present, alternative is neonatal transplantation as proposed by the group at Loma Linda in California [44]. Throughout the years, some cardiologists continued to be advocates of conservative "comfort care" for neonates with HLHS; however, with survival rates of about >70% being achieved in many centers, these infants are no longer being written off as untreatable. Now the question is more about the quality of survival, especially intellectual development. It is also recognized that many have both chromosomal and non-chromosomal anomalies that affect the cerebral and gastrointestinal systems [45].

As was the case from the beginning of pediatric cardiac surgery, this new patient population presented a new management dilemma for the anesthesiologist that required a solution before acceptable operative results could be achieved. Patients with HLHS were hemodynamically unstable prior to CPB because of the large volume load on the heart coupled with coronary artery supply insufficiency. The coronary arteries in HLHS are supplied by the PDA in a retrograde fashion through a hypoplastic ascending and transverse aorta that terminates as a single "main" coronary artery. A common event at sternotomy and exposure of the heart was VF secondary to mechanical stimulation. This fibrillation was sometimes intractable, necessitating emergent CPB during internal cardiac massage. This was not an auspicious beginning to a major investigational open-heart procedure.

It was during these years that there was a transition from morphine–halothane–N_2O maintenance to a high-dose narcotic technique (fentanyl or sufentanil) combined with 100% oxygen. This technique seemed to provide some protection against sudden VF events compared with historical controls [46]. Despite this modest progress in getting patients successfully onto CPB, it soon became painfully clear that not much progress was made in treating this lesion when trying to wean the patients from bypass. The infants were still unstable coming off bypass and severely hypoxemic, and it took some time before we discovered a way to deal with the problem.

A chance observation led to a solution. Infants who came off bypass with low PaO_2 (around 30 mmHg) after the HLHS repair often did well, while those with immediate "excellent gases" ($PaO_2 \geq 40$–50 mmHg) became progressively unstable in the ICU a couple of hours later, developing severe metabolic acidosis and dying within the first 24 hours. This observation, combined with discussions with the cardiologists about PVR and systemic vascular resistance (SVR), led to attempts to influence these resistances to assure adequate systemic flow. In retrospect, infants with low PaO_2 after bypass had smaller aortopulmonary shunts and adequate systemic blood flow, while those with larger shunts and higher initial PaO_2 levels after weaning from bypass tended to "steal" systemic blood flow through the shunt. This would occur in the postoperative period, as the PVR that initially remained elevated as a result of CPB returned to more normal levels. These observations led to the technique of lowering the FiO_2 (sometimes as low as 0.21) and allowing hypoventilation in order to increase PVR in patients with larger shunts so as to supply adequate systemic blood flow [46]. A different technique used at other institutions to deal with this problem was to add CO_2 to the anesthetic gas flow, increasing PVR and continuing to use "normal ventilation" in children who had excessive pulmonary blood flow in the setting of larger shunts [47]. Both techniques represented different approaches to the same problem: finding ways to deal with the need to carefully balance PVR and SVR after bypass in a fragile parallel circulation where dynamic changes in ventricular function were taking place.

These observations, and the subsequent modifications in anesthetic and postoperative management, improved the survival for the stage I palliation (Norwood procedure). It should be noted that the pediatric cardiac anesthesiologist was a fully contributing partner in the progressive improvement in the outcome of this very complex and challenging lesion. More importantly, the techniques developed and the knowledge gained in this process also simplified the management of other patients with parallel circulation and SV physiology. The obvious example is truncus arteriosus, where the "usual" ST-segment depression and frequent VF that occurred intraoperatively can almost always be avoided. Any decrease in PVR during anesthesia in a child with unrepaired truncus arteriosus can lead to pulmonary "steal" of systemic blood flow and decreased diastolic pressure through the common trunk to the aorta and PA, resulting in hypotension and insufficient systemic blood flow expressed initially as coronary insufficiency and ST depression (or elevation).

During the same decade, the surgical treatment of transposition of the great arteries (TGA) underwent several changes. The Mustard variant of the atrial switch operation was feared due to the risk of SVC obstruction. The arterial pressure during bypass and in the immediate post-bypass period in the OR tended to be low and the pressure in the SVC high. Following a Mustard procedure, it was not uncommon to see a child with a grotesquely swollen head having to be taken back to the OR for immediate reoperation. Venous hypertension in the internal jugular veins and SVC led to low cerebral perfusion pressure during CPB with many of these children suffering brain damage, especially when reoperation was delayed. The extent and prevalence of such damage were never systematically studied. An article from Great Ormond Street in London

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demonstrated arrested hydrocephalus in Mustard patients [48]. The Senning operation (another variant of the atrial switch approach to TGA) was better but traded pulmonary venous obstruction for systemic venous obstruction. When the diagnosis was not promptly made and intervened upon, these infants were often quite sick by the time they came to reoperation.

The successful application of the arterial switch operation (ASO) as described by Jatene in 1975 revolutionized the surgical management of TGA [49]. The ASO eliminated the risk of pulmonary and systemic venous obstruction seen with atrial level switches. It also diminished the incidence of the subsequent sick sinus syndrome, a later complication thought to result from the extensive atrial suture lines required by these earlier repairs. The introduction of the ASO again heavily involved anesthesiologists. At many institutions, the learning curve was very steep with the initial ASOs performed resulting in a substantial number of infants with severe myocardial ischemia or frank infarcts. This was due to a variety of problems with the coronary artery transfer and reimplantation onto the "switched" aorta that had been moved to the left ventricle outflow tract. Pediatric cardiac anesthesiologists gained extensive experience with intraoperative pressor and inotropic support as well as nitroglycerin infusions. They were expected by surgeons to provide the support necessary to get infants through what later turned out to be iatrogenic myocardial ischemia. As surgeons refined coronary artery transfers, these problems largely disappeared, along with the need for major pressor and inotropic support as well as for nitroglycerin infusions inappropriately directed at major mechanical obstructions in the coronary arterial supply. At many centers, the ASO is now largely considered to be a "routine" procedure which presents, for the most part, no unique anesthetic challenges.

It was also during this period that a randomized controlled study of the stress response in infants undergoing cardiac surgery while anesthetized with high-dose sufentanil was performed. It showed that a high-dose narcotic technique suppresses but does not abolish stress responses. It also demonstrated a reduction in morbidity and possibly mortality [50]. However, when the study was refined 10 years later using only high-dose narcotic anesthesia techniques, no mortality differences were seen between various high-dose narcotic techniques. It must be pointed out that the patient population was older and the bypass technique had undergone some refinement [51].

Fontan and the catheterization laboratory: 1990–2000

As the neonatal palliation of HLHS and other SV lesions improved and became more commonplace, a growing number of patients became candidates for the Fontan operation. The Fontan operation, HOWEVER, became somewhat problematic as it was applied to younger patients with an increasing variety of SV CHD. Although many of the patients had technically perfect Fontan operations, they developed low cardiac output with massive pleural and pericardial effusions postoperatively in the cardiac ICU. Many died in the postoperative period. Their course over the first 24–48 hours was relentlessly downward and could only be reversed by taking them back to the OR, reversing the Fontan operation, and reconstructing a systemic to PA shunt. It was hard for the caretakers of these infants to accept the loss of children they had known from birth. Various treatment modalities were tried to avoid this sequence of events, from early extubation to the use of a G-suit to improve venous return to the heart. In some centers, a large balloon was placed tightly around the child's lower body and intermittently inflated by a Bird respirator asynchronous with ventilation.

After a couple of years, two innovations changed both management and prognosis. Both were linked to the understanding that a major limitation of the Fontan operation was the need for a normal or near-normal PVR to allow survival through the postoperative period and that CPB, when used, causes a marked elevation of PVR in the early postoperative period through the release of inflammatory mediators and cytokines. This bypass-related increase in PVR was associated with younger age (<2 years old) at the time of Fontan completion – the higher baseline PVR of the infant made the bypass-related increase in PVR worse. This resulted in inadequate pulmonary blood flow and (single) ventricular filling in the early postoperative period, leading to a cycle of low cardiac output, pulmonary and systemic edema, further increases in PVR, acidosis, and death.

One solution was to interpose a bidirectional (Glenn) cavopulmonary anastomosis as the second stage of palliation 6–12 months before completion of the Fontan. This procedure and the related operation known as a "hemi-Fontan," directed only half of the systemic venous return through the lungs at a time when the infant's PVR had not yet fallen to normal levels. By doing so, it preserved an alternative pathway for (single) ventricular filling by the systemic venous return not routed through the lungs. This enabled the patients to maintain reasonable cardiac output, although they were a bit "blue" during the early postoperative period when the PVR was elevated by CPB. The other innovation was the "fenestrated" Fontan where a small fenestration in the atrial baffle allowed systemic venous return to bypass the lungs as a right-to-left shunt, thereby maintaining ventricular filling and systemic cardiac output during the early postoperative period of high PVR. Over time, the fenestration closed as PVR fell and shunting decreased. Alternatively, a device delivered during an interventional cardiac catheterization could close the fenestration [52]. The process of testing the applicability of the Fontan principle and its various modifications involved a great deal of collaborative work among anesthesiologists, surgeons, and cardiologists, the net result of which was that the prognosis for a patient with HLHS, and indeed for all children with SV defects, greatly improved. As these improvements spread and were amplified by work done in other centers, local improvement became national and international.

Within institutions, this multidisciplinary collaborative effort spread naturally to the cardiac catheterization laboratory. Previously, nurses sedated children, operating under the supervision of the cardiologist performing the

Table 1.1 Cardiovascular surgery at Boston Children's Hospital

	Total cases			
	1982 (*N* = 538)	**2008 (*N* = 942)**	**2014 (*N* = 1,127)**	**2019 (*N* = 1,190)**
AAOCA			0.6%	1.1%
Valve repairs and replacements				
AoV plasty/replacement			0.9/1.4%	3.6/0.7%
AVV plasty/replacement			10.3/1.9%	11.3/1.3%
Septal defects				
VSD repair	12%	7.5%	7.3%	5.6%
ASD repair	9.6%	8.6%	6.0%	6.0%
CAVC[a]	5.9%	4%	3.6%	2.8%
DORV			0.6%	0.7%
Cavopulmonary connection				
Fontan procedure	3%	5.4%	4.2%	3.4%
Bidirectional Glenn		3.1%	3.2%	3.2%
Systemic outflow obstruction				
Coarctation/Arch	7.7%	5.1%	4.5%	6.3%
LVOT repair	11.7%	13.8%	4.2%	2.4%
Norwood procedure/stage 1	3%	2.5%	3.5%	1.5%
Biventricular repair[b]			0.4%	4.6%
Pulmonary outflow obstruction				
Tetralogy of Fallot repair	7.6%	6.8%	7.7%	4.5%
PA/VSD			1.6%	1.6%
Conduit placement/revision	2.8%	2.3%	2.4%	2.2%
Other RVOT reconstruction	1.6%	9%	5.8%	3.9%
Pacemaker, ICD placement	5%	3.8%	4.6%	5.6%
Patent ductus arteriosus	8%	6.2%	3.9%	2.1%
Transposition of great arteries		5.6%	3.6%	4.3%
Miscellaneous[c]	15%	16.1%		21.2%

AAOCA, anomalous aortic origin of a coronary artery; AoV, aortic valve; ASD, atrial septal defect; AVV, atrioventricular valve; CAVC, complete atrioventricular canal; ICD, internal cardiac defibrillator; LVOT, left ventricular outflow tract; PA/VSD, pulmonary atresia/ventricular septal defect; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

[a] CAVC includes partial/transitional atrioventricular septal defects.

[b] Biventricular repair includes 1.5 ventricle repair, biventricular recruitment, and biventricular repair.

[c] Includes pulmonary vein stenosis repair, cardiac tumors.

catheterization procedures. In many institutions, this involved high volumes of cases sedated by specially trained nurses, while in others with smaller pediatric caseloads, the practice of using general anesthesia for children undergoing cardiac catheterizations had been routine. As pediatric cardiologists began to develop interventional procedures, the need for greater control and support of hemodynamics and respiratory function became apparent. The interventional cardiologists increasingly turned to pediatric cardiac anesthesiologists to help manage these patients while the cardiologists themselves dealt with the complex demands of carrying out interventional procedures in infants and children with CHD. As was the case with the newly devised pediatric cardiac surgical procedures, the development of interventional procedures for CHD in the cardiac catheterization laboratory posed a novel set of challenges for the pediatric cardiac anesthesiologist. Not the least of these was providing anesthesia and hemodynamic support in the dark, foreign environment of the cardiac catheterization laboratory. The introduction of increasingly complex (e.g. vessel and valve dilations, miniaturized closure devices, transcatheter valves) and hemodynamically significant procedures placed progressively greater demands on the anesthesiologists, who became more integrally involved in these procedures.

The application and expansion of interventional electrophysiology procedures in the pediatric patient population further illustrate the progressive complexity encountered by anesthesiologists. When radiofrequency ablation procedures were exclusively employed in the management of paroxysmal atrial tachycardia (PAT) in healthy teenagers with structurally normal hearts, the anesthesia care was straightforward. Now, in contrast, many of these procedures are performed in children (or adults) with complex CHD (unrepaired, repaired, or partially palliated) and varying levels of cyanosis and cardiac output.

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Despite these innovations, the defects encountered have remained largely the same (Table 1.1). Two notable exceptions are the decrease in PDA ligations (neonates as small as 700 gm are now candidates for catheter-based closure) and the increase in biventricular repairs that likely represent shifting treatment paradigms and changing referral patterns [53]. As Helen Taussig remarked in her paper about the global distribution of cardiac diagnoses, only surgical interventions change the numbers [54].

Emergence of new technology – imaging (TEE, MRI) and ECMO: 2000–2010

The first decade of the 21st century saw numerous changes driven by the availability of new imaging technology, including transesophageal echocardiography (TEE) and cardiac MRI. The utility of TEE in congenital heart surgery was first demonstrated in the late 1980s by several groups in Japan and the United States, including Russell and Cahalan at the University of California, San Francisco. The use of two-dimensional echocardiography, as well as three-dimensional echocardiography, improved diagnosis both within and outside the OR. Utilizing TEE to interpret the anatomy of complex CHD and to judge the adequacy of intraoperative repairs is considerably more challenging in pediatric patients with CHD than in adults with acquired heart disease. Many centers have called upon pediatric echocardiographers to make such judgments, rather than make the pediatric cardiac anesthesiologist responsible for TEE imaging as well as the management of the patient in the post-bypass period. The use of TEE has also expanded to the cardiac catheterization laboratory where it is used in parallel with fluoroscopy for device closure of septal defects and transcatheter valve placement, allowing for confirmation of the placement and location of the device [55]. It has likewise been useful in guiding the implantation of mechanical support devices, especially the ventricular assist device (VAD), confirming cannula placement and the absence of obstruction [56]. The main concerns for the anesthesiologist while using TEE remain oropharyngeal and/or esophageal trauma, airway obstruction, left atrial pressure alternation, and inadvertent extubation of the child in the middle of an operation "under the drapes."

Similarly, the emerging availability of cardiac MRI (cMRI) and its expanded use for the diagnosis and follow-up of CHD patients continue to challenge the congenital cardiac anesthesiologist. Although seen by many on the multidisciplinary care team as a simple, non-invasive procedure, cMRIs involve relatively long anesthetics in a magnetic field with limited patient access and are often performed in patients with severe, complex CHD.

The early 2000s also saw increased utilization of another technical innovation of great importance to pediatric cardiac anesthesia – extracorporeal membrane oxygenation (ECMO) (Figure 1.4). First described in pediatric cardiogenic shock (2-year-old s/p Mustard) and neonatal respiratory failure in 1974 and 1976, respectively, ECMO use increased during the early 2000s due to expanded pediatric inclusion criteria as well as increased use in children with CHD, during extracorporeal cardiopulmonary resuscitation (ECPR), during failure to wean from CPB, and a bridge to transplantation [57–62]. In the history of the development of pediatric cardiac anesthesia, we have come a long way from the baby in the ice bath being prepared for DHCA to the complex technology necessary for ECMO resuscitation.



Figure 1.4 Infant on extracorporeal membrane oxygenation in the cardiac intensive care unit.

The surgical and interventional management of CHD continues to evolve as surgeons and interventional cardiologists further develop and refine treatment approaches that cross the boundaries of traditional CHD care. Two such novel treatment modalities, intrauterine fetal cardiac catheter intervention (see Chapter 19) and the hybrid stage I Norwood palliation (see Chapter 30), were first described in humans in the early 2000s. The hybrid stage I palliation in the catheterization laboratory requires the anesthesiologist to anticipate and treat significant hemodynamic perturbations, blood loss, and arrhythmias while managing neonatal SV physiology without CPB and providing an anesthetic technique that offers the possibility of early tracheal extubation [63, 64]. Hybrid surgical procedures are increasing in the catheterization laboratory and include VSD closure, HLHS management, and percutaneous valve implantation. They require a multidisciplinary approach and the availability of cardiac interventionists, cardiac surgeons, and anesthesiologists [65].

2011–2021 and the future

With the understanding that certain cardiac lesions are progressive in nature, prenatal intervention is believed to halt the process *in utero* and improve the postnatal outcome of these patients. Since the initiation of fetal cardiac interventions, the number of these procedures has been increasing and includes valvuloplasty of the aortic and

pulmonary valve, balloon atrial septostomy for restrictive or intact interatrial septum in cases of HLHS and TGA, and fetal pacing in complete heart block. Improving delivery of oxygenated blood to the brain *in utero* may affect neurodevelopmental outcomes of patients with congenital disease – an area of interest and research [66, 67]. Pediatric cardiac anesthesiologists have an integral role in planning for and carrying out these procedures. Fetal cardiac intervention for aortic valve stenosis or HLHS with intact atrial septum requires the anesthesia team(s) to provide anesthesia for the pregnant mother and the fetus with the fetus monitored by ultrasound throughout [68]. The success of the intrauterine procedures potentially allows for the growth of the hypoplastic ventricle such that a biventricular repair is possible during infancy. Although the reported success of these procedures is promising, the number of cases and series published is small and does not allow us to conclude superiority over neonatal surgeries or to discuss long-term outcomes at this time [69, 70]. Studies comparing anesthetic techniques are likewise limited with most having been done in animal models. Prospective clinical trials in human fetuses would have multiple limitations, including the limited number and type of procedures, their associated complications, the maternal condition, and the lack of time to assess the fetal outcomes during the procedure itself [71].

In the past decade, extracorporeal life support (ECLS) has also evolved. Although ECMO remains the most widely used type of ELCS across centers, additional ventricular support devices have been introduced as a bridge to transplant, leading to an increase in the number of patients listed for pediatric cardiac transplant [72]. The EXCOR® pediatric VAD (Berlin Heart GmbH, The Woodlands, TX, United States) was approved by the US Food and Drug Administration in December 2011. A database study from 2007 to 2011 (the date of approval of the device) compared the 1-year post-transplant survival between patients who underwent heart transplant without VAD support and those who were bridged with EXCOR to transplant; it showed that the pediatric patients supported with EXCOR have similar survival rates to Open Procurement and Transplantation Network status 1A patients supported on either inotropes or ventilator [73]. Pre-transplant mechanical support with a VAD has been shown to offer a post-transplant survival advantage when compared to support with ECMO [74]. Children with ECLS awaiting cardiac transplantation may present for multiple procedures while awaiting transplantation. Periprocedural challenges include perioperative anticoagulation management, appropriate monitoring, and the maintenance of hemodynamic stability [75–77]. It is imperative that the care team is familiar with the device, the patient's settings, and how the adjustment of the settings affects hemodynamics. A team approach, including a surgeon, intensivist, anesthesiologist, and mechanical support team, is of the utmost importance.

As survival has dramatically improved over the years, attention has gradually shifted from the reduction of mortality to the reduction of perioperative and long-term morbidity. Recent concerns about the effect of anesthetic agents on the developing brain have prompted extensive efforts to study the magnitude and mechanism of the effect as well as whether alternative agents or protective strategies are warranted [78]. Neonatal cardiac surgery occurs at a particularly vulnerable age and exposes the patient to a number of potentially injurious factors including cyanosis, CPB, inflammation, low cardiac output, and/or mechanical support devices. The neurodevelopmental outcome was found impaired in approximately one-third of children who underwent surgery at a neonatal age [79]. It has been shown that 23–40% of neonates presenting with a complex cardiac defect show evidence of cerebral injury on preoperative MRI [80–84]. Postoperatively, 36–73% of patients have evidence of new cerebral lesions on MRI [80–86]. Cardiac anesthesiologists may play a key role in the minimization of perioperative neurologic injury and have been involved in research to identify risk factors and ameliorate their deleterious effects on neurodevelopmental outcomes [87–89]. The American Heart Association/American Academy of Pediatrics guidelines on the evaluation and management of neurodevelopmental outcomes in children with CHD now identify brain biomarkers and EEG measurements that could be useful in managing patients during the perioperative period [90, 91].

Quality improvement and perioperative cost reduction have also come under the purview of the congenital cardiac anesthesiologist, providing new challenges and opportunities for the current generation of anesthesiologists. The development and adoption of Enhanced Recovery After Surgery (ERAS) protocols for cardiac surgery, and more specifically, for pediatric cardiac surgery, have generated a great deal of interest in recent years [92]. These protocols generally include minimization of *nil per os* (NPO) time, incorporation of multimodal analgesia regimens, and clinical optimization for early extubation, mobilization, and ICU discharge. Such changes in care have associated risks that will require careful, ongoing assessment considering the advantages achieved with postoperative ventilation and sedation. For example, the incidence of arrhythmias and cardiac arrest following endotracheal suctioning in the ICU postoperatively was greatly diminished with the use of heavy sedation with fentanyl that prevented major swings in PA pressure [93, 94]. Careful selection of patients for early extubation and judicious use of shorter-acting anesthetic agents may allow lengths of stay to be shortened without increasing risks. Other advances, such as limiting the total dose of anesthetic agents by developing ways to monitor the depth of anesthesia, so as to give sufficient doses to prevent awareness but still attenuate the stress response to CPB, are being explored, but remain elusive [95].

In recent years, there has been an increasing call for the regionalization of CHD care, both in the United States and around the world [96, 97]. CHD care within the United States is highly fragmented and there exists a high degree of variability in staffing, program structure, care processes, case volumes, and outcomes. At present, within the United States, there is no national mandate for the regionalization of pediatric cardiac care. A regionalization simulation by Welke et al. suggested that the consolidation of care from 153 hospitals with varying case volumes to 37 hospitals with case volumes

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of >300 cases/year would increase mean travel distance by 31 miles, but lead to a decrease of 263 deaths, 124,602 hospital days, and 1,504 major complications over a 4-year period [98]. Challenges such as changes to staffing, revenue generation considerations, effects on post-graduate medical education, and care coordination will have to be better understood before regionalization could become a viable tool for quality improvement.

Another area of growing interest is the development of cross-center collaboration in order to share data and expertise so as to help establish best practices, reduce practice variation, and shift the mean toward better outcomes. Numerous organizations, consortiums, and collaboratives [Society of Thoracic Surgeons (STS), Pediatric Cardiac Critical Care Consortium (PC^4), Congenital Cardiac Anesthesia Society (CCAS), Pediatric Acute Care Cardiology Collaborative (PAC^3), the American College of Cardiology's IMPACT Registry®, National Pediatric Cardiology – Quality Improvement Collaborative (NPC-QIC), Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs), Extracorporeal Life Support Organization (ELSO), Pediatric Heart Transplant Society (PHTS), Cardiac Neurodevelopmental Outcome Collaborative (CNOC), Advanced Cardiac Therapies Improving Outcomes Network (ACTION)] have been established to maintain multicenter registries of pediatric cardiovascular data. Collaborative projects have the potential to lead to profound improvements in outcomes as well as reduced costs. Since 2010, the CCAS has maintained an anesthesia database, and currently, more than 60 centers submit anesthetic data, and there are more than 100,000 anesthetics represented in the data. Together with the 120 centers submitting surgical data, this collaborative approach has led to publications about airway management and extubation practices, dexmedetomidine usage, bleeding and thrombosis, and vascular access practices [99–104]. Benchmarking by individual centers in comparison to all contributing centers for adverse outcomes is also made possible by this collaboration as a quality and outcomes tool.

Congenital heart disease – a growing specialty from the fetus to the adult patient

Tempora mutantur et nos in illis – "Time changes and we develop with time." It has been over 80 years since Robert Gross first ligated a PDA and we have seen amazing developments in the treatment of CHD. Indeed today, surgical ligation of PDAs is increasingly uncommon as devices and approaches for percutaneous PDA occlusion have developed even for the smallest premature infants [105]. Concomitantly, anesthesiology has evolved and slowly defined pediatric anesthesia, and then cardiac anesthesia, and now, in the past two decades, pediatric cardiac anesthesia has developed as a distinct and separate area of subspecialization. Freisen documents the landmark publications from the 1930s to 2010s that have documented and disseminated the new knowledge that has continuously advanced the field [106].

In 2005, the Congenital Cardiac Anesthesia Society (CCAS; www.pedsanesthesia.org/ccas) in the United States was formed and now has more than 1,300 members. It provides a forum for subspecialized educational meetings, a national database of congenital cardiac anesthesia cases (see Chapter 3), and recommends standards for training. Starting in 2010, leaders of the CCAS proposed a curriculum for a 12-month fellowship in pediatric cardiac anesthesia, defined case numbers in 2012, in 2014 further refined the curriculum, and in 2018 proposed a detailed set of milestones for training in the field [107–109]. These efforts culminated in the recognition of the postgraduate training in pediatric cardiac anesthesia by the Accreditation Council for Graduate Medical Education in the United States in 2021 [110] (see Chapter 2). CCAS is a society organized within the larger Society for Pediatric Anesthesia, indicating that this specialty has chosen to align itself more closely with pediatric anesthesiology than with adult cardiac anesthesiology, although there are important common interests and principles in all three of these specialties caring for patients with CHD.

As part of the trend of increasing long-term survival, the patient care group growing most rapidly at most centers is the adult with CHD. The prevalence of adults in the year 2000 was 49% of patients with CHD [111]. This is the somewhat unexpected result as care in childhood improves and more and more of these patients survive to adulthood and even into old age. At many institutions, special programs have been created to treat these patients and the problems they face. These problems include complications, reoperations, and socioeconomic barriers to normal education, employment, and the creation of families. The question of pregnancy and anesthetic management of delivery for these patients is also evolving. It is unclear who is most qualified to provide anesthesia for such patients during labor and delivery. But suddenly the pediatric cardiac anesthesiologist may find themselves having to care for adults [112–114] (see Chapter 20).

Although there has been much progress in pediatric cardiac anesthesia in providing safe anesthetic care and improving the outcome of treatment of CHD in the OR and catheterization laboratory for patients of all ages, much remains to be done. One can say with certainty that the intimate connection between advances in therapy, surgical or medical, and the anesthesia support services required to make those therapeutic advances possible will continue to present new challenges to the pediatric cardiac anesthesiologist (Figure 1.5). The pediatric cardiac anesthesiologists will, in turn, meet those challenges and in the process find ways to make yet more improvements. Thus, we progress in our art and science.

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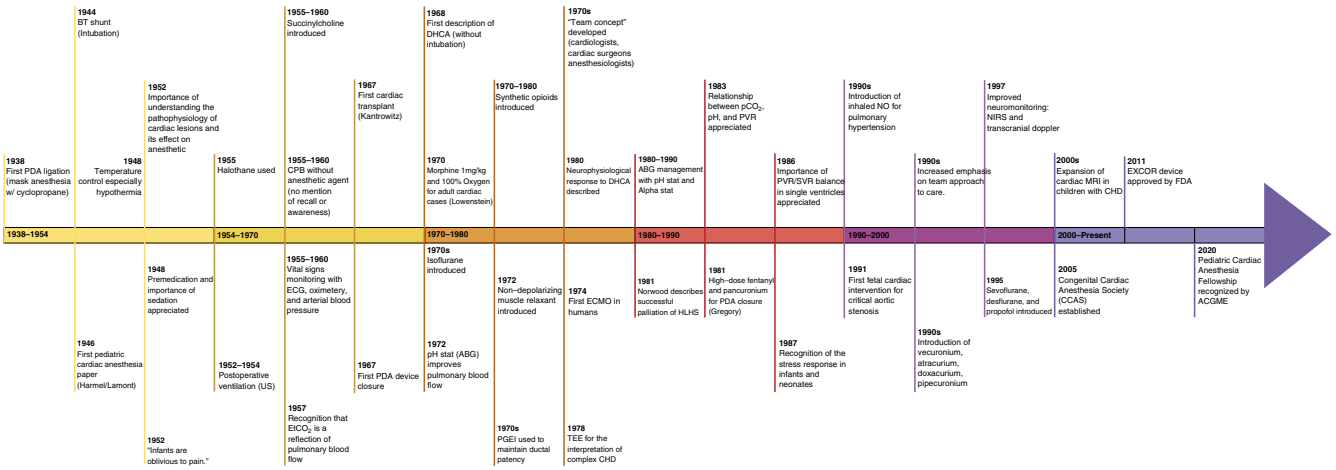


Figure 1.5 Milestones in the anesthetic management of patients with congenital heart disease. ABG, arterial blood gas; ASD, atrial septal defect; ACGME, Accreditation Council for Graduate Medical Education; BT, Blalock–Taussig; DHCA, deep hypothermic circulatory arrest ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; $EtCO_2$, end-tidal carbon dioxide; EXCOR, extracorporeal ventricular assist device; FDA, Food and Drug Administration; HLHS, hypoplastic left heart syndrome; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; NO, nitric oxide; PDA, patent ductus arteriosus; PCO_2, partial pressure of carbon dioxide; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; US, United States; U/S, ultrasound.

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Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

5 Harmel MH, Lamont A. Anesthesia in the surgical treatment of congenital pulmonic stenosis. Anesthesiology 1946;7:477–98.
Describes the perioperative experience of administering 103 anesthestics to 100 patients undergoing surgical treatment of congenital pulmonic stenosis with Drs. Blalock and Taussig.

13 Ketas AS, Kurosu Y, Telford J, Cooley DA. Anesthetic problems in cardiopulmonary bypass for open-heart surgery. Experiences with 200 patients. Anesthesiology 1958;19:501–14.
Describes the anesthetic problems and management of 200 patients who underwent total cardiopulmonary bypass for intracardiac surgery.

19 Odegard KC, Rockoff MA. The "Mother of pediatric cardiac anesthesia": an interview with Dr. Dolly D. Hansen, a pioneering woman in medicine. Paediatr Anaesth 2020;30:964–9.
A wonderful interview with Dr. Hansen detailing the events surrounding cardiac surgery and anesthesia at Boston Children's Hospital from the 1970s to 1990s, including the first Norwood Stage I palliation, first use of deep hypothermic circulatory arrest at the hospital, and use of the hyperbaric chamber for pediatric cardiac surgery.

25 Greeley WJ, Kern FH, Ungerleider RM, et al. The effect of hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral metabolism in neonates, infants, and children. J Thorac Cardiovasc Surg 1991;101:783–94.
Compares patients undergoing moderate hypothermic bypass (28°), deep hypothermic bypass (18–20°), and deep hypothermic circulatory arrest (18°). It estimates ischemic tolerance times and suggests an exponential relationship of temperature on bypass and cerebral metabolism.

29 Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery. Effects on the stress response. Lancet 1987;1:243–8.
RCT of preterm babies undergoing patent ductus arteriosus ligation with nitrous oxide and d-tubocurarine with or without fentanyl (10 mcg/kg IV). Babies that received fentanyl had a significantly lessened hormonal stress response to surgery as well as less circulatory and metabolic complications post-operatively.

35 Heymann MA. Pharmacologic use of prostaglandin E1 in infant with congenital heart disease. Am Heart J 1981;101:837–43.
Progress report on the therapeutic use of prostaglandins in neonatal cardiac malformations.

43 Norwood WI, Lang P, Hansen DD. Physiologic repair of aortic atresia-hypoplastic left heart syndrome. N Engl J Med 1983;308:23–6.
Case report describing the first patient that underwent physiologically corrective surgery as part of a new program of staged surgical management of neonatal hypoplastic left heart syndrome.

70 Mäkikallio K, McElhinney DB, Levine JC, et al. Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome. Patient selection for fetal intervention. Circulation 2006;113:1401–5.
Identifies mid-gestation echocardiographic features associated with progression of fetal aortic stenosis to hypoplastic left heart syndrome in an attempt to refine patient selection for fetal intervention.

90 Marino BS, Lipkin PH, Newburger JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation 2012;126:1143–72.
American Heart Association and Academy of Pediatrics review of the literature addressing developmental disorder/disability and developmental delay in the congenital heart disease population. Presents an algorithm for the surveillance, screening, reevaluation, and management of developmental disorder or disability for providers who care for patients with congenital heart disease.

106 Friesen RH. Landmark papers in pediatric cardiac anesthesia: documenting the history of the specialty. Paediatr Anaesth 2016;26:1047–52.
An excellent review of important papers published from 1930s to 2010s, organized into anesthetic risk, cardiovascular effects of anesthetics, control of pulmonary vascular resistance, bypass and coagulopathy, and neurodevelopmental disability.

111 Marelli AJ, Ionescu-Ittu R, Mackie AS, et al. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation 2014;130:749–56.
Estimates congenital heart disease prevalence in infants, children, and adults using population-based date sources though 2010, illustrating the growing proportion of the congenital heart disease population comprised of adults.

CHAPTER 2

Education for Anesthesia in Patients with Congenital Cardiac Disease

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Introduction

Pediatric cardiac anesthesiology has developed as a sub-subspecialty of anesthesiology over the past 50 years. It has been practiced since the first patent ductus arteriosus (PDA) was ligated by the cardiac surgeon Dr. Robert Gross in 1938. Initially, in the 1970s and 1980s, anesthesiologists interested in practicing pediatric cardiac anesthesia would spend additional months during residency training or as a staff member gaining experience in anesthesia care for these patients, the apprenticeship model. With further advances in surgical and catheter-based interventions and technologies in patients with congenital heart disease (CHD), pediatric cardiac anesthesiology has evolved in parallel with pediatric cardiac surgery and pediatric cardiology as a distinct field. The evolution of this specialty has led to the establishment in 2005 of a dedicated professional society, the Congenital Cardiac Anesthesia Society (CCAS).

Before the advent of CCAS, there were very few resources in terms of providing training and experience in the specific field of pediatric cardiac anesthesia. The board of directors along with other pediatric anesthesiologists addressed the lack of training criteria in congenital cardiac anesthesia and have developed the resources that we have today culminated in recognition by ACGME [1].

Why teach and learn congenital cardiac anesthesia?

Pediatric cardiac anesthesiology encompasses the care of neonates, infants, children, and adults with CHD and pediatric patients with acquired heart disease. Initially, practitioners interested in the field used to spend varying amounts of additional training time during their anesthesiology residency or as faculty members. However, the fields of congenital cardiac surgery and congenital cardiology have made significant strides which required ever-increasing advances in the anesthetic care of these patients. While the subspecialty initially grew in concert with pediatric anesthesiology and adult cardiac anesthesiology programs, pediatric cardiac anesthesiology is now a distinct field which requires a unique fund of knowledge and skillset beyond that possessed by either the pediatric anesthesiologist or adult cardiac anesthesiologist alone.

In order to successfully care for patients with CHD and pediatric patients with acquired heart disease, it is necessary to gain expertise in the perioperative care of all forms of CHD from the simple to the most complex, and the pediatric acquired heart lesions. This includes a comprehensive understanding of congenital and acquired cardiovascular anatomy and pathophysiology. In addition, mastery of patient care along the continuum of care from the preoperative planning

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period, through the operative procedure itself, and through the postoperative recovery must be appreciated. In light of the wide spectrum of congenital cardiovascular anomalies and each condition having unique management considerations, the pediatric cardiac anesthesiologist must be adept at developing and executing an individualized perioperative anesthetic plan. Importantly, pediatric cardiac anesthesiologists must also master complex procedural skills to care for these patients with abnormal anatomy and physiology which go beyond those used to care for the patient with a normal cardiovascular system.

Today, an estimated 40,000 live births/year in the United States are affected with CHD [2]. These patients present for cardiac and noncardiac procedures. Given the increasing demands for well-trained pediatric cardiac anesthesiologists, it is essential that a cohort of comprehensively trained practitioners of this craft be consistently produced. This is the only viable pathway to further advance the key objectives of providing improved clinical care and enhanced patient safety [3–5].

The current model

In 2010, leaders in pediatric cardiac anesthesiology in the United States recognized the need for a standardized educational approach to the training of pediatric cardiac anesthesiologists, and accordingly several program guidelines were developed [6]. In 2014, the Pediatric Anesthesia Leadership Council (PALC) in conjunction with the CCAS recognized the need for a formalized training pathway [7]. They specifically recommended that pediatric cardiac anesthesiology be an additional 12-month second-year advanced fellowship following pediatric anesthesia. This recommendation clearly recognizes that attaining skills to become a competent pediatric cardiac anesthesiologist requires training beyond a standard pediatric anesthesia fellowship. In 2018, specific training milestones required during fellowship training were established by the CCAS leadership [8].

At present, the total number of 12-month positions offered is 28. Figure 2.1A and B represent the number of programs and trainees over time. While the structure of these fellowship programs mostly follows the published guidelines as noted above, it is acknowledged by CCAS leadership, program directors, and individual pediatric cardiac anesthesiologists that central oversight of program quality is needed for educational and training consistency. Hence, as cardiology and cardiac surgery have done previously, the subspecialty has moved forward, aiming for a standardized approach to fellowship training with ACGME oversight (Figure 2.2).

Pediatric cardiac anesthesia training

Curriculum development should employ a logical, systematic approach linked to specific healthcare needs. The Kern model of curriculum development for medical education could be used to develop a curriculum to teach and learn congenital cardiothoracic anesthesia [9]. This has a six-step approach and consists of the following:

1. Problem identification and general needs assessment
2. Targeted needs assessment
3. Goals and objectives
4. Educational strategies
5. Implementation
6. Evaluation and feedback.

Problem identification and general needs assessment

This comprises identification and characterization of the healthcare problem:

- Whom does it affect?
- What does it affect?
- What is the qualitative and quantitative importance of the effects?

As detailed above, education in anesthesia for CHD covers a wide range of lesions – uncorrected, corrected, and palliative therapies. The trainee needs to be educated in all aspects of the six core competencies related to these topics.

The following points should be addressed to obtain adequate needs assessment:

- What proficiencies (cognitive, affective, and psychomotor skills) currently exist among learners?

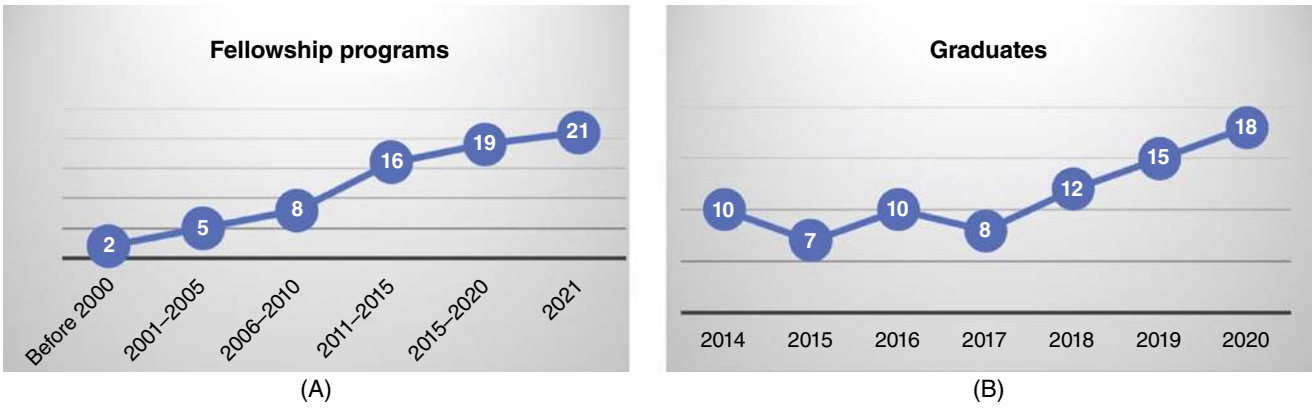


Figure 2.1 (A) Number of pediatric cardiac anesthesia programs over time; (B) number of graduating 12-month fellows per year over time.

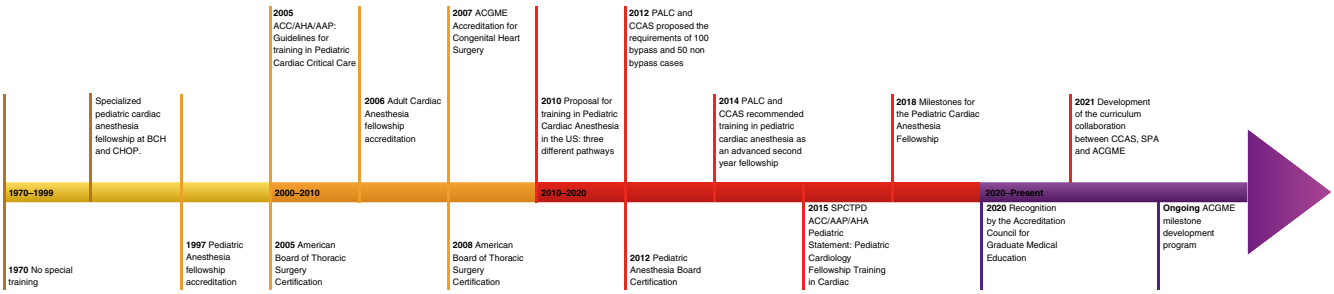


Figure 2.2 Timeline of major milestones in education and training in CHD. AAP, American Academy of Pediatrics; ACC, American College of Cardiology; ACGME, Accreditation Council for Graduate Medical Education; AHA, American Heart Association; BCH, Boston Children's Hospital; CCAS, Congenital Cardiac Anesthesia Society; CHOP, Children's Hospital of Philadelphia; PALC, Pediatric Anesthesia Leadership Council; SPA, Society for Pediatric Anesthesia; SPCTPD, Society of Pediatric Cardiology Training Program Directors; US, United States.

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- Previous training and experiences of fellows and residents in congenital cardiac anesthesia
- Current training and experiences already planned for trainees
- Resources available to learners (patients and clinical experiences, information resources, computers, audiovisual equipment, role models, teachers, mentors)
- Perceived deficiencies and learning needs
- Characteristics of the learners and barriers to learning and teaching.

The current state of the pediatric cardiac anesthesia training in CHD was most recently characterized in an email survey performed in 2019 addressed to program directors (n = 19). The number of pediatric cardiac anesthesia programs in the United States offering pediatric cardiac anesthesiology training has continually grown from 2 in 2000 to 8 in 2010 and to 19 in 2020 (Figure 2.1A). Similarly, the number of 12-month fellows graduating each year has increased (Figure 2.1B).

Following graduation, the majority of trainees (75%) work either exclusively as a pediatric cardiac anesthesiologist or divide their time as a general pediatric anesthesiologist and as a pediatric cardiac anesthesiologist. Seven percent work in combined pediatric cardiac and adult cardiac anesthesia programs. The remaining 15% work in a combination of anesthesia and critical care, adult cardiac anesthesia, or other settings.

Targeted needs assessment

For the needs assessment to be an accurate reflection of what is required, it must involve the current trainees (learners) in pediatric cardiac anesthesia. Attempts should be made to assess the current strengths and weaknesses in knowledge, skills, and performance [10]. The environment in which education is currently happening needs to be evaluated as well. Is the operating room (OR) conducive to the education of some of the complex physiology or should the initial education happen in a simulated environment where the stress level of all concerned is much lower? It is vital that all the stakeholders (trainees, program directors, cardiologists, intensivists, and pediatric cardiac surgeons) are involved in the development at an early stage. Barriers and reinforcing factors that affect learning should be identified early on. Faculty development programs may be necessary to improve the quality of teaching and education in congenital cardiac anesthesia. Needs assessment should also include what resources are currently available to the trainees to facilitate learning in congenital cardiac anesthesia.

There is a dedicated body of science, knowledge, and skills related to the unique field of pediatric cardiac anesthesiology. There are chapters on the practice of pediatric cardiac anesthesia in every major anesthesia textbook, every major pediatric anesthesia textbook, and in several major cardiac surgical and pediatric interventional catheterization/electrophysiology textbooks. More importantly, there are numerous textbooks devoted entirely to the practice of pediatric cardiac anesthesia. In addition to textbooks and journals, dedicated pediatric cardiac anesthesia faculty at all the different respective programs constitute a body of knowledge and a source of education for the fellows in the field.

The case mix in the training programs, multidisciplinary faculty educators, and access to online journals and educational materials, including the availability of audiovisual equipment, are vital to the success of curricular delivery. The value of the hidden and informal curriculum that is currently in place should not be underestimated.

Goals and objectives

Goals and objectives must, by necessity, be specific and measurable. They should measure the knowledge (cognitive), attitude (affective), and competence (psychomotor) of the learners. The goals and objectives are currently being developed by a task force which is comprised of ACGME leadership, a pediatric anesthesiologist, an adult cardiac anesthesiologist, and representative from the Society for Pediatric Anesthesia and CCAS. The goals and objectives should reflect the relationship of the educational process to the degree of participation of the learners, as well as the faculty response to the developed curriculum. To achieve goals, the program must be structured to ensure optimal patient care while providing trainees with the opportunity to develop skills in clinical care, judgment, teaching, and research. Consideration should be given to the use of learning goal-scoring rubrics. Meyerson et al. performed needs assessment for an errors-based curriculum on thoracoscopic lobectomy and structured the curriculum based on their observations using a standardized checklist [11].

The following goals and objectives are valuable in the OR to achieve competency in congenital cardiac anesthesia:

- The subspecialist in congenital cardiac anesthesiology should be proficient in providing anesthesia care for both pediatric and adult patients undergoing congenital cardiac and vascular surgery as well as anesthesia for non-cardiac surgery.
- The subspecialist should demonstrate and conduct a preoperative patient evaluation; and demonstrate the ability to interpret imaging, cardiovascular, and pulmonary diagnostic test data.
- The subspecialist should be able to evaluate and understand the anesthetic management of patients undergoing non-operative diagnostic and interventional cardiac, thoracic, and electrophysiological procedures. Examples include angiography, arrhythmia mapping and ablation, stent placements, and device closures.
- The clinical curriculum should include competency and demonstrate cognitive proficiency in the management of cardiopulmonary bypass (CPB), pharmacological and mechanical hemodynamic support as well as extracorporeal circulation.
- The subspecialist should be able to create a plan for postoperative critical care, including ventilatory support, extracorporeal circulatory support, and pharmacologic hemodynamic support, as well as understand the implications of pain management.
- The subspecialist should demonstrate effective communication skills in obtaining informed consent from families, discussing any complications that may have occurred as well as providing consultations as and when necessary.
- The subspecialist should demonstrate skills in preparing materials and presenting at multidisciplinary conferences to allied health professionals.

- The subspecialist must demonstrate professionalism in the work environment as evidenced by the ability to show compassionate care to the patient and their diverse needs, respecting other providers, as well as complying with program, department, and institutional policies and procedures.
- The subspecialist should understand the value of multidisciplinary teams, be able to evaluate errors, and find solutions, thereby enhancing patient safety and improving outcomes for their patients.

The didactic curriculum provided through lectures, conferences, and workshops should supplement clinical experience as necessary for the fellow to acquire the knowledge to care for cardiothoracic patients with CHD and conditions outlined in the guidelines for the minimum clinical experience for each fellow. The didactic components should include the areas in the following list, with an emphasis on how cardiothoracic diseases affect the administration of anesthesia and life support to cardiothoracic patients with CHD.

These represent guidelines for the minimum didactic experience for each fellow:

- Embryological and morphological development of the cardiothoracic structures; nomenclature of CHD
- Pathophysiology, pharmacology, and clinical management of patients with all adult and pediatric CHD, including single ventricle lesions, septal defects, defects of semilunar and atrioventricular valves, left- and right-sided obstructive lesions, transposition of the great vessels, defects of systemic and pulmonary venous return, cardiomyopathies, vascular rings, and tracheal lesions
- Pathophysiology, pharmacology, and clinical management of patients requiring heart, lung, and heart-lung transplantation, including immunosuppressant regimes and selection criteria
- Non-invasive cardiovascular evaluation: electrocardiography, echocardiography, cardiovascular computed tomography (CT), and magnetic resonance imaging (MRI)
- Cardiac catheterization procedures and diagnostic interpretation; invasive cardiac catheterization procedures, including balloon dilatations and stent placement; device closure of septal defects, PDA and baffle leaks, and arrhythmia ablation
- Pre-anesthetic evaluation and preparation of pediatric and adult cardiothoracic patients
- Pharmacokinetics and pharmacodynamics of medications prescribed for medical management of pediatric and adult cardiothoracic patients
- Peri-anesthetic monitoring methods, both non-invasive and invasive, including use of ultrasound guidance: intra-arterial, central venous, mixed venous saturation, cardiac output determination, transesophageal and epicardial echocardiography, neurological monitoring, including near-infrared cerebral oximetry, transcranial Doppler, and processed electroencephalograms
- Pharmacokinetics and pharmacodynamics of anesthetic medications prescribed for cardiothoracic patients. Pharmacokinetics and pharmacodynamics of medications prescribed for the management of hemodynamic instability: inotropes, chronotropes, vasoconstrictors, vasodilators
- Extracorporeal circulation (including CPB, low-flow CPB, deep hypothermic circulatory arrest, antegrade cerebral perfusion, extracorporeal membrane oxygenation (ECMO)), myocardial preservation, effects of extracorporeal circulation on pharmacokinetics and pharmacodynamics, cardiothoracic, respiratory, neurological, metabolic, endocrine, hematological, renal, and thermoregulatory effects of extracorporeal circulation and coagulation/anticoagulation before, during, and after extracorporeal circulation
- Circulatory-assist devices: left and right ventricular assist devices and biventricular assist devices
- Pacemaker and automated internal cardiac defibrillator (AICD) insertion and modes of action
- Perioperative ventilator management: intraoperative anesthetic and critical care unit ventilators and techniques
- Postanesthetic critical care of pediatric cardiothoracic surgical patients
- Pain management of pediatric and adult cardiothoracic surgical patients. Post-anesthetic critical care of pediatric and adult cardiothoracic surgical patients
- Research methodology and statistical analysis
- Quality assurance and improvement
- Ethical and legal issues
- Practice management

What is the minimum level of anesthesia training required?

- Subspecialty training in congenital cardiac anesthesiology should begin after satisfactory completion of a residency program in anesthesiology accredited by the ACGME or other training judged suitable by the program director and
- Trainees should complete an ACGME-accredited pediatric anesthesia fellowship of 12 months' duration after anesthesia residency.
- Alternatively, the trainees could enter the training following completion of an ACGME-accredited adult cardiac anesthesia fellowship of 12 months' duration after anesthesia residency if they have completed additional pediatric anesthesia rotations.

What are the ideal duration, case quantity, and scope of training?

The following represent suggested cases for the minimum clinical scope and duration of training:

- Nine months of clinical anesthesia activity caring for patients with congenital cardiac problems in the OR, the cardiac catheterization laboratory, and other locations.
- This experience should include a minimum of 100 anesthetic procedures, the majority of which must require CPB. At least 50 of these patients should be infants from birth to 1 year of age and should include at least 25 neonates (≤1 month of age). The trainee should also care for at least 25 adults (≥18 years of age).
- This experience should also include a minimum of 50 patients undergoing diagnostic procedures (cardiac catheterization, echocardiography, MRI, etc.), as well as

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therapeutic procedures in the catheterization laboratory (arrhythmia ablation, pacemaker insertion, septal defect closure, and valve dilatation, etc.)
- Suggested case numbers for specific lesions are described in Table 2.1 [12]
- Adequate experience should be obtained in the preoperative evaluation of pediatric and adult cardiothoracic patients.
- The fellow should understand how to use information from diagnostic studies and how to recognize when additional studies and/or consultations are indicated.

It is important to note that formal guidelines and case numbers are currently being developed by the ACGME task force. They will be available by end of 2021.

Table 2.1 Suggested case numbers for Anesthetic Management of Surgical Repairs and Diagnostic and Interventional Procedures

Surgical cases bypass	**Case numbers**
Hypoplastic left heart syndrome	3
Transposition of great arteries	3
Total anomalous pulmonary venous return	1
Common atrioventricular canal	6
Tetralogy of Fallot	5
Ventricular/atrial septal defect	10
Bidirectional Glenn	5
Fontan	4
Left ventricular assist device	1
Right-sided valvular lesions	15
Left-sided valvular lesions	15
Heart/lung transplant	2
Interrupted aortic arch	1
Truncus arteriosus	1
Surgical cases without bypass	**Case numbers**
Blalock-Taussig shunt	3
Aortic coarctation	3
Patent ductus arteriosus	3
Vascular ring	2
Diagnostic and interventional (catheterization laboratory and imaging)	**Case numbers**
Hemodynamic catheterizations	20
Pulmonary artery dilations	7
Pulmonary vein dilations	5
Endomyocardial biopsy	5
Transcatheter valve placement	2
Device closure (atrial septal defect/ventricular septal defect/PDA)	2
Emergency cath cases (neonatal AS or PS, balloon atrial septostomy, stenting of Blalock-Taussig/Sano shunts)	3
Electrophysiology studies	10
Cardiac magnetic resonance imaging/chest tomography	2
Sedated transthoracic or transesophageal echocardiography	5
Cases with extracorporeal support (extracorporeal membrane oxygenation)	2

Source: Nasr et al. [11]. Reproduced with permission from Elsevier.

Relationship to other anesthesiology programs

The congenital cardiac anesthesiology program should function in direct association with one of the following ACGME-accredited programs, preferably within the same institution: core anesthesiology, adult cardiothoracic anesthesiology, or pediatric anesthesiology. A congenital cardiac anesthesiology program may be conducted in either a general hospital or a children's hospital. The division of responsibilities between trainees in the core anesthesiology program and an associated fellowship program(s) in adult cardiothoracic anesthesiology and/or pediatric anesthesiology must be clearly delineated. The presence of congenital cardiac anesthesiology fellows must not compromise the clinical experience and number of cases available to pediatric anesthesiology fellows and/or core anesthesiology residents. There must be close cooperation between the core anesthesiology program, the adult cardiothoracic anesthesiology program and/or the pediatric anesthesiology program, and the congenital cardiac anesthesiology program.

Educational strategies

Educational strategies involve the content of materials to be delivered in the setting of the curriculum as well as the instructional methodology to be used to deliver the content. It will be beneficial to have the fellows involved in the planning of the educational activity. Consideration should be given to forming a committee of responsible faculty members to ensure that the best possible content is delivered.

Content of the curriculum

The driving force here is the learning objectives that have been created in the goals and objectives section. The program director should consider the development of a syllabus that includes learning objectives for the lectures, locations of the lectures, any readings that may have to be completed prior to arrival at the educational activity as well as additional resources for the educational activity. All of this information could be made available on a departmental intranet so the fellows have access to it at all times of the day (example: Open Pediatrics; https://www.openpediatrics.org).

Educational methodology

To thrive in today's technologically complex and information-laden clinical environment, pediatric cardiac anesthesiology trainees must become self-directed learners who are able to engage in self-reflection and assessment of their learning needs. To facilitate self-directed learning, program directors and trainees should work together to develop individualized educational plans, learning contracts, and milestone timelines. Here is a list of suggested educational strategies that may be used to address the cognitive, affective, and psychomotor objectives of the curriculum:
- Strategies for achieving cognitive objectives
  - Readings
  - Lectures or large group interactive discussions
  - Audiovisual materials

- Small group discussions
- Self-study modules or web-based learning materials
- Online discussion forums
- Podcasts or streaming video
- Fellow-led didactic sessions
- Systematic reading of stored transesophageal echocardiogram (TEE) clips, if included in the curriculum

- Strategies for achieving objectives effectively
  - Exposure to, and discussion of, challenging clinical and ethical situations
  - Simulated-learning and cross-training experiences with facilitated debriefing to gain experience in leadership, communication, task delegation, and team development skills
  - Facilitation and modeling of openness, introspection, and reflection through the establishment of a safe learning environment
  - Observation of role models, and serving as a role model for anesthesiology residents
  - Standardized patients and role plays
- Strategies for achieving psychomotor objectives
  - Regular supervised clinical experiences with feedback
  - Simulations: partial task trainers, full-body manikins, virtual reality simulators
  - Audiovisual reviews of skills
  - Expert-derived checklists of procedural competence.

In the digital age, there are several tools available to deliver content to the learners. However, all the different methods available may not be suitable for the various objectives to be achieved. The use of self-directed readings, lectures, programmed learning, small group discussions, problem-based discussions, and learning projects is helpful to advance cognitive knowledge. Team-based training, problem-based learning, and participation in learning projects all help to cultivate problem-solving skills. However, to teach some of the affective objectives, reflective exercises, discussions, and observing role models in the OR may be helpful. To teach skills or competency objectives, the trainee may be taught using simulations, using standardized patients, supervised clinical experiences, artificial models, and role playing. All these methods of teaching have pros and cons. They have to be adapted for each individual program and only serve as a guide for program directors. The ideal methodology will encourage active learning, provide immediate feedback to the trainee, promote learning from experience, provide a safe learning environment, facilitate learning of higher cognitive objectives, and promote trainee motivation and responsibility. The utilization of low-cost and less resource-heavy methodologies is also more likely to succeed. Consideration should be given to faculty development if new instructional methodologies are to be utilized.

Conferences should be regularly attended by the trainee, including lectures, interactive conferences, hands-on workshops, morbidity and mortality conferences, cardiac catheterization conferences, echocardiography conferences, cardiothoracic surgery case review conferences, journal reviews, and research seminars. While the faculty members should be the leaders of the majority of the sessions, active participation by the fellow in the planning and production of these conferences is essential. Attendance at multidisciplinary conferences, especially in cardiovascular medicine, pulmonary medicine, cardiothoracic surgery, vascular surgery, and pediatrics relevant to cardiothoracic anesthesiology, should be encouraged. Provision of an opportunity for fellows to participate in research or other scholarly activities is vital to the success of the educational strategies employed. The fellows must be encouraged to complete a minimum of one academic assignment. Projects may include grand rounds presentations, preparation and publication of review articles, book chapters, and manuals for teaching or clinical practice, clinical research investigation, or similar scholarly activities. A faculty supervisor must oversee each project.

In the context of practice-based learning and improvement, trainees should be encouraged to participate in audits of their own patient care and be involved in critical appraisal of clinical practices and the literature. Trainees should be encouraged to develop learning portfolios as well as to create a learning plan for themselves. Learner-driven teaching methodologies are likely to be more successful.

Congenital cardiac anesthesia lends itself nicely to education in the various aspects of systems-based practice and teamwork. Trainees should be involved with quality improvement and attend case conferences focused on cost-effectiveness, patient safety, and quality of care as part of a multidisciplinary team. *In situ* team training has been associated with improved patient outcomes in the setting of pediatric emergencies.

Explicit education in professionalism in the cardiothoracic OR should be promoted by educating the trainees using faculty role models, trainee participation in writing professionalism goals and objectives, and trainee participation in ethics rounds in the intensive care unit (ICU) as part of a multidisciplinary team.

The use of the Internet to share educational materials is becoming the norm. As the number of physicians training to be providers of anesthesia for CHD is small, this option is attractive to allow for sharing of information between programs. Interesting case discussions, sharing of echocardiographic images, and recent articles pertaining to this area could be posted on the Internet as well. The MedEdPORTAL (https://www.mededportal.org), Health Education Assets Library (HEAL) (https://mwdl.org/collections/HealthEducationAssetsLibraryHEAL.php), Open Pediatrics (https://www.openpediatrics.org), CCAS website (https://pedsanesthesia.org/partner-organizations-sections/ccas), and Multimedia Educational Resource for Learning and Online Teaching (https://www.merlot.org/merlot) are some currently available resources that could house the curricular material related to congenital cardiac anesthesia. However, given this wealth of potential educational resources, it is important to keep in mind that the learner should be physically and mentally involved in the learning process.

The use of simulation in medical education continues to grow. Simulation allows complex clinical tasks to be broken down into their parts. Simulation-based medical education can contribute considerably to improving medical care by boosting medical professionals' performance and enhancing patient safety. Many surgical specialties are looking to simulation as a method for teaching and learning as well as evaluation. There is a role for simulation in learning procedural skills, especially in the climate of decreasing clinical exposure. A recent meta-analysis of the use of simulation in

anesthesia training showed inconsistency in the measurement of non-technical skills and consistency in the (ineffective) design of debriefing [13]. More recent studies have demonstrated that adjunctive simulation-based curriculum enhances learners' management of clinical scenarios [14]. There is also evidence in the surgical literature that virtual reality training can improve OR performance. In a recent meta-analysis, a simulation-based airway management curriculum appeared superior to no intervention and non-simulation intervention for important educational outcomes. Consideration should be given to the use of a clinical skills laboratory to pre-teach some of the skills necessary in the management of a complex patient population [15]. Leaders in pediatric anesthesiology also advocate the use of a shared simulation-based curriculum to improve education opportunities for fellowship programs, especially in light of the small size of many of them [16].

Anesthesia for CHD is a high-risk, low-error tolerance field. The fundamental knowledge and skills that congenital cardiac anesthesiologists will need to master if they are to increase their capacity to attain higher levels of performance are considerable. A clinical microsystems model may prove useful to facilitate the development of this fundamental knowledge and skills using the action-learning theory and sound education principles to provide the opportunity to learn, test, and gain some degree of mastery.

Implementation

Once a curriculum has been developed, it is the role of the program director to oversee its successful implementation. Success is achieved through insightful leadership, transparency and constant communication, forethought and general administration of the program, continuous quality improvement efforts, and establishment and maintenance of a stable educational environment. The program director must possess the requisite specialty expertise and have the relevant training and/or clinical experience in providing anesthesia care for congenital cardiac surgical patients that meet or exceed that associated with completion of a 1-year congenital cardiac anesthesiology fellowship program. To implement a new curriculum, the program director must possess the necessary administrative and educational knowledge and skills to:

- Identify necessary materials and resources
- Obtain administrative and, if necessary, financial support
- Identify and recruit qualified faculty members
- Provide faculty development and teacher training
- Develop administrative mechanisms to support the curriculum
- Identify appropriate teaching space (e.g. in the OR, simulation center, or other appropriate clinical venues)
- Anticipate and address barriers.

Above all else, the program director is responsible for keeping faculty, learners, and staff informed about plans for implementing a new curriculum. Individuals who are expected to support, teach, or participate in a program must be made aware of the program's design, educational strategies, and assessment methods in order to ensure its smooth execution. The program director should also present curricular updates, especially any successes or milestones achieved, to identified stakeholders. Stakeholders are people with an interest in the program and its evaluation and may include the pediatric anesthesia department chair, cardiothoracic anesthesia division chief, anesthesia residency program director, other anesthesia subspecialty fellowship directors, funding agencies, and/or hospital administrators (e.g. the Vice President for Quality and Safety).

While the program director is responsible for overseeing the curriculum, this does not have to be done in isolation. There are a number of faculty and staff members who can provide support and advice regarding the design and teaching of a curriculum. As an added benefit, those involved at the front end of a program's design and implementation are more likely to want to participate in teaching and assessing the curriculum. A junior faculty member with expertise in congenital cardiac anesthesiology and interest in medical education may be eager to help develop and present a curriculum. Pediatric anesthesia faculty members with previous curriculum development experience as well as clinician educators committed to anesthesiology training in CHD may be recruited as educational consultants and then asked to teach in the program. Involving other faculty members in the development and implementation of a curriculum also ensures a program's continuity, stability, and sustainability.

There are several key decisions that must be made, and steps that must be taken, before implementing a congenital cardiac anesthesia curriculum. First, the program director needs to decide whether to introduce the curriculum as a pilot program, in stages or to present it in its entirety. There are arguments both for and against each approach; however, if stakeholders are wary of a new curriculum's educational benefit, it is best to introduce a pilot program in order to collect evidence of its value and then gain support for its full implementation. Recruiting faculty members and then developing them to teach in the program are further essential steps. To present a successful and sustainable curriculum, there must be a sufficient number of faculty members with documented qualifications to instruct and adequately supervise all anesthesia fellows in the program. Although the number of faculty members involved in teaching will vary, there should be at least three, and these should be equal to or greater than two full-time equivalents, including the program director. A ratio of no less than one full-time equivalent faculty member to one subspecialty fellow must be maintained. The anesthesia faculty must possess the requisite congenital cardiac anesthesia specialty expertise, competence in clinical care, and teaching abilities, as well as documented educational and administrative abilities and experience in their field. There must be evidence of active participation by qualified physicians with training and/or expertise in congenital cardiac anesthesiology beyond the requirement for completion of a core anesthesiology residency. The faculty members should have training and experience that would generally meet or exceed that associated with the completion of a 1-year congenital cardiac anesthesiology program. Faculty members in cardiology, cardiothoracic surgery, pediatrics, intensive care, and pulmonary medicine can provide teaching in multidisciplinary conferences. The responsibility for establishing and maintaining an environment of inquiry and scholarship of discovery, dissemination, and application rests with the program director and the faculty, and an active research component must be included in each program.

Equally important to recruiting qualified faculty members with the appropriate expertise and training in congenital cardiac anesthesiology is the development of their ability to teach the curriculum. It is a common error to assume that faculty members with the necessary clinical skills, knowledge and specialized expertise are also qualified to teach. They are rarely required to provide documentation of their teaching experience or evidence of teacher training, even for the most basic skills such as assessing and providing feedback to learners, leaving many ill-prepared for their teaching responsibilities. The core components of a faculty development program in training congenital cardiac anesthesiology fellows should include:

- Communication of curricular goals and objectives
- Discussion of qualities that characterize effective and respected clinical educators
- Suggestions of how to apply adult learning principles to congenital cardiac anesthesia clinical venues
- Assurance that faculty members can effectively assess trainees and provide useful feedback on their performance
- Review of best teaching practices for common educational strategies such as procedural teaching as well as large and small group facilitation skills
- Specialized training sessions to teach faculty members how to communicate and explain clinical decision-making; make teaching in the OR a priority; maintain a balance between supervision and autonomy; promote critical thinking skills; and provide clear, constructive, and developmental feedback.

Evaluation and feedback

Evaluation and feedback are essential for the continuous improvement and development of a curriculum. The purpose of evaluation in medical education is to determine if the curricular goals and objectives have been met. In addition, an evaluation can determine if the time, resources, and effort spent producing the curriculum are merited. Evaluation results can be used to identify educational outcomes, assess teaching effectiveness, determine areas of strength and needed improvement, and make decisions about the level of support necessary to sustain or further develop a curriculum. "Feedback" is defined as the provision of information regarding an individual's or program's performance to trainees, faculty, stakeholders, and accrediting agencies. While the terms "evaluation" and "assessment" are often used interchangeably when measuring both individual learner and program outcomes, it is best to distinguish between them, adopting the term "evaluation" in relation to the measurement of the curriculum, and "assessment" in relation to the measurement of learners. As learner assessment often comprises a significant portion of a program's evaluation, making this distinction will help to avoid confusion when planning and presenting results [17].

The process of curriculum evaluation and feedback

To conduct a comprehensive evaluation of a congenital cardiac anesthesiology program, multiple sources of data must be sought, which requires a systematic information collection process involving learners, faculty, other healthcare providers, and, in some cases, external evaluators. Data and information should be collected at the start of a curriculum, -its midpoint, conclusion, and subsequent to completion (e.g. 6–12 months post-fellowship). A program director's effort in collecting evaluation data at the program's mid- and end-points will be less challenging if the requisite time and effort are put into creating specific and measurable learning objectives at the start of a curriculum, and into assessing the fellows' knowledge, skills, and performance levels in congenital cardiac anesthesiology up-front. With the appropriate administrative support, a program director can institute an iterative "plan–do–check–act" methodological approach to continuous curriculum improvement. This method involves *planning* (the curriculum development steps 1 through 4 – problem identification through educational strategies); *doing* (the implementation step); *checking*, in which data are collected to determine what is going well and what needs to be improved moving forward; and *acting*, in which the program director addresses identified curricular problems by determining their causes and applying countermeasures, standardizes what is working well, and communicates decisions, new standards and improvements to be made.

Kirkpatrick [18] described four levels to focus program evaluation, which Curran and Fleet [19] later adapted for use in medical education evaluation:

- Reaction – this level of evaluation is intended to evaluate how well participants liked a program. It generally provides data concerning participants' perceptions, and satisfaction with objectives, content, instruction, delivery, and/or instructors.
- Learning outcomes – this level of evaluation involves some form of assessment of changes in skills, knowledge, or attitudes among learners; it is most commonly conducted through pre-and post-test study designs.
- Performance improvement – this level of evaluation provides information on the extent to which learning has influenced the post-learning behavior or performance of learners in their practice setting. Evaluating at this level attempts to answer the question: Are the newly acquired skills, knowledge, or attitudes being used in the everyday environment of the learner?
- Patient/health outcomes – this level of evaluation is concerned with measuring tangible results which are influenced by the performance of the learner as a result of participation in the educational activity. These tangible results can be transferred to a health perspective (e.g. improving patient health or improving efficiencies). Evaluation at this level is challenging given the variety of uncontrollable variables a learner encounters when he or she leaves an educational program.

A program director needs first to determine the intention of the curriculum evaluation as well as the audience reviewing the results in order to choose which level(s) to focus his or her time and effort on. For example, if a department chair is mostly interested in whether the fellows are better able to perform advanced TEE in the OR, then evaluation results should report on learning outcomes. If, however, the Vice President of Healthcare Quality is interested to report to the board on the reduction of anesthesia-related complications post-CHD surgery, then the focus should be on patient/health outcomes.

Learner assessment methods

With the adoption of outcomes-based training requirements in 2002, the focus of learner assessment for all residency programs has been on the ACGME's six core competencies. The goal of competency-based assessment is for trainees to meet discreet, transparent, achievable objectives at developmentally appropriate stages in training. The challenge for program directors of congenital cardiac anesthesia training programs is to ensure that the curriculum's goals and objectives match the intended competencies.

Learner assessment should be thought of in terms of formative and summative purposes. Formative assessment should be provided consistently throughout a fellowship program, as it provides trainees with feedback on their performance towards defined educational objectives. It also steers learning towards desired outcomes and can focus high-achieving learners towards more rapid skill advancement. The summative assessment determines how well learners achieved competency of specific objectives at developmentally appropriate stages in their training. These are conducted at the end of a rotation or program.

For formative and summative learner assessment to be considered reliable, performance data must be obtained from the predominant clinical units where congenital cardiac anesthesia trainees work and learn. Multidisciplinary cardiothoracic team members, including supervising anesthesiologists, surgeons, nurses, and other staff members in the OR or ICUs, should use multiple assessment methods and tools (e.g. standardized checklists, performance audits, case logs), in combination with the trainee's own self-assessment, to create a comprehensive performance appraisal system required in a competency-based training model.

Learner assessment methods can be categorized as cognitive, affective, or psychomotor appraisals. Cognitive learner assessment methods are used to determine and provide feedback about trainees' acquisition and application of biomedical, clinical, epidemiological, and social-behavioral sciences knowledge, as well as their ability to problem-solve, reason through clinical challenges, and use critical thinking skills. Methods include:

- Written or computer-interactive tests – multiple-choice, essay-type questions
- Oral examinations
- Questionnaires
- Individual interviews
- Procedural, operative, or case logs
- Chart stimulated recall
- Review of scholarly projects and research
- Observation of a fellow's ability to apply data from advanced monitoring devices.

Affective learner assessment methods are used to appraise and provided feedback about trainees' attitudes, feelings, motivations, and decisions. Methods include the following:

- Standardized patient exercises
- Questionnaires
- Written reflections and essays
- Rating and forced ranking forms
- Patient and family surveys
- Teamwork exercises
- Peer assessment of professionalism
- Case-based discussions that involve clinical uncertainty or ethical dilemmas
- Individual interviews
- Self-report of adverse events and near misses related to pediatric cardiothoracic and vascular anesthesia rotations
- Root cause analyses of medical errors or complications of patients under the fellows' care.

Psychomotor learner assessment methods are used to appraise and provide feedback on trainees' physical skills or the performance of actions. There are numerous methods to use for psychomotor assessment. Methods must be criterion-based, anchored using demonstrable behaviors, and developmentally appropriate. The most common methods are as follows:

- Simulation exercises
- Portfolios of videotapes
- Direct observation of discrete procedural skills (such as intubation or line placement)
- Objective structured clinical examinations
- Objective structured assessment of technical skills
- Mini-clinical evaluation exercise
- Clinical encounter cards
- Clinical work sampling
- Practice metrics scoring using data collected as part of routine care via an existing perioperative information management system (e.g. central line insertion and temperature management).

The assessment process for congenital cardiac anesthesia trainees should emphasize learning, inspire confidence in the trainee, enhance the trainee's ability to self-monitor, and drive the institutions toward self-assessment and curricular change when necessary. The primary endpoint should be the ability to demonstrate trainee competence in the care of their patients in accordance with the ACGME's six core competencies – patient care, medical knowledge, systems-based practice, professionalism, interpersonal and communication skills, and practice-based learning and improvement.

In 2018, the CCAS published a consensus statement for the milestones of the ACGME based on the six core competencies [8] (Table 2.2). Milestones are "specialty specific achievements that residents are expected to demonstrate at established intervals as they progress through training" [20, 21].

Program evaluation methods

Curriculum developers perform an evaluation of an educational program to make judgments about its successes and deficiencies; decide about resource allocation, administrative support, and material management; determine teaching performance; uncover influencing attitudes regarding the curriculum's educational value; pinpoint areas that are effective and that are in need of improvement, conclude whether the curriculum met its intended learning goals and objectives and should continue to be incorporated into a training program.

A core component of the program evaluation process is to conduct and collect data from formative and summative learner assessment methods. The faculty must evaluate in a timely manner the fellows whom they supervise. In addition, the fellowship program must demonstrate that it has

Table 2.2 Core competencies and milestones for the pediatric cardiac anesthesia fellowship

Six core competencies and milestones
Patient care [4]
Perioperative assessment, planning and management
Technical/Procedural Skills
Understanding cardiovascular surgical procedures
Understanding cardiac catheter-based therapeutic procedures and electrophysiologic studies
Medical knowledge [4]
Congenital and acquired cardiovascular anatomy, physiology and pathophysiology
Pharmacology
Cardiopulmonary bypass, extracorporeal circulation and circulatory assist device principles
Understanding cardiac diagnostic procedures (e.g., echocardiography, magnetic resonance imaging, cardiac catheterization, computerized tomography)
Systems-based practice [3]
Coordination of care
Incorporation of patient safety and quality improvement into clinical practice
Understanding of health care economics; cost awareness and cost-benefit analysis
Practice-based learning and improvement [2]
Self-directed learning and scholarly activity
Education of team members and other health care providers
Professionalism [3]
Commitment to institution, department and colleagues
Receiving and giving feedback
Responsibility to maintain personal, emotional, physical and mental health
Interpersonal and communications skills [2]
Communication with patients and families
Interprofessional communication and transitions of care

Source: Nasr et al. [8]. Reproduced with permission from Wolters Kluwer Health, Inc.

an effective mechanism for assessing fellow performance throughout the program and utilizes the results to improve fellow performance. At the minimum, faculty members responsible for teaching must provide a critical assessment of the six ACGME core competencies for each fellow at the end of 6 and 12 months of training. Learner assessment should include regular and timely performance feedback to fellows that includes at least semi-annual written evaluations. Such evaluations should be communicated to each fellow in a timely manner and be maintained in a record that is accessible to each fellow. The program director or designee must inform each fellow of the results of the evaluations at least every 6 months during training, advise the fellow of areas needing improvement, and document the communication. Assessments should include the fellows' fund of knowledge, clinical judgment and clinical psychomotor skills, patient management skills, and the ability to critically analyze complex clinical situations. Periodic evaluation of patient safety and teamwork is mandatory. Evidence of the congenital cardiac anesthesiology fellows' scholarly projects and research, including those pertaining to continuous quality improvement and risk management, should be reviewed and summarized by designated faculty mentors.

The program director should conduct a final evaluation for each fellow who completes the program. This evaluation must include a review of the fellow's performance during the final period of education and should verify that the fellow has demonstrated sufficient professional ability to practice competently and independently. Documentation of the congenital cardiac anesthesiology fellows' successful completion of the program as well as subsequent training or career plans should be kept up to date, as this information will help to inform future program evaluation efforts. A program director should also maintain a listing of all graduating fellows' scholarly activities as well as aggregate feedback from the ACGME's resident fellow surveys. This survey provides feedback on the duty hours, faculty supervision and instruction, fellow evaluation processes, educational content and resources, patient safety and teamwork, as well as overall reflections on the quality of the training program.

Faculty members

As part of a comprehensive curriculum evaluation effort, faculty members should be evaluated on their congenital cardiac anesthesia teaching performance and supervisory capabilities. Clinical teaching assessment instruments should produce valid and reliable results and any findings should be provided to faculty members in a clear and concise format. The faculty members should be assessed on their medical knowledge, clinical competence, teaching effectiveness, scholarly activities, and professional attributes. Lombarts et al. found that existing tools could be adapted for the systematic evaluation and support of faculty members involved in residency programs. They suggest basing faculty evaluation on qualities established by the well-known Stanford Faculty Development Program instrument. These qualities include the establishment of an effective learning climate, professional attitudes towards trainees, communication of goals, evaluation of trainees, and quality of feedback provided. Moreover, Baker's study of resident assessment of educators in anesthesiology provides data about the positive impact that trainee evaluation can have in motivating clinicians to become better teachers [22].

Overall program effectiveness

Summative program evaluation provides information on the degree to which a curriculum has met its intended objectives and at what cost. It can also document the curriculum's success in engaging and motivating its learners and faculty as well as associated subspecialty anesthesiology training programs. In addition to quantitative data, summative program evaluation may include qualitative information about educational barriers and unanticipated obstacles as well as means to streamline curriculum implementation. The results of summative program evaluations are often disseminated to stakeholders to obtain or maintain time, administrative support, funding, and other resources. The educational

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effectiveness of a program must be evaluated at least annually in a systematic manner.

Representative program personnel (at a minimum the program director, representative faculty, and one fellow) must be organized annually to review program goals and objectives, and the effectiveness with which they are achieved. In the evaluation process, the group must take into consideration written comments from the faculty, the most recent report of the graduate medical education committee of the sponsoring institution, and the fellows' confidential written evaluations. If deficiencies are found, the group should prepare an explicit plan of action, which should be approved by the faculty and documented in the minutes of the meeting.

The program should use fellow performance and outcome assessment in its evaluation of the educational effectiveness of the fellowship program. The performance of program graduates in the certification examination should be used as one measure of evaluating program effectiveness. The program should maintain a process for using assessment results together with results of other program evaluations to improve the fellowship program.

Curriculum maintenance and enhancement

Once a curriculum in congenital cardiac anesthesia has been developed, the next challenge is curriculum maintenance. A successful curriculum is continually developing by responding "to evaluation results and feedback, to changes in knowledge base and the material requiring mastery, to changes in resources (including faculty), to changes in its targeted learners, and to changes in institutional and societal values and needs". Areas for curricular enhancement may include a review of the written or intended curriculum, assessment of the environment/setting of the curriculum, and determination of learner assessment methods to meet new accrediting agency requirements (such as the ACGME's milestones). The following data can be collected and utilized to assess how well a curriculum is functioning:

- Program evaluation
- Learner/faculty/patient questionnaires
- Patient quality metrics
- Objective measures of learners' skills and performance
- Focus group of learners, faculty, staff, and patients
- Other systematically collected data
- Regular/periodic meetings with learners and faculty
- Special retreats and strategic planning sessions
- Site visits
- Informal observation of curricular components, learners, faculty, and staff
- Informal discussions with learners, faculty, and staff

Congenital cardiac anesthesia is a subspecialty in which there are significant interactions between anesthesiologists and cardiac surgeons, cardiologists, radiologists, and other pediatric subspecialists. Close alliance between these disciplines is vital to the growth and development of the subspecialty. Furthermore, curriculum enrichment is dependent on both intra- and inter-subspecialty collaboration as well as combined faculty development efforts.

Dissemination

There is a need for an international comprehensive curriculum in congenital cardiac anesthesia. Local adaptation of a core curriculum will be necessary to overcome technological and cultural care delivery obstacles. The following issues should be considered when considering the dissemination of core curriculum material:

- What material should be disseminated?
- How should the material be disseminated (publications, presentations, multi-institutional interest groups or academic societies, educational clearing houses, online learning systems, digital communication, instructional videotapes or audiotapes, and/or instructional computer software)?
- What resources are required (time and effort, personnel, equipment/facilities, funds)?
- How can dissemination and impact be measured?

Dissemination of a curriculum can be a valuable process, benefiting many other congenital cardiac anesthesia trainees. A coherent strategy must be determined on what should be disseminated, appropriate methods of dissemination, and the best use of limited time and administrative resources.

Role of professional societies

At present, the CCAS, in conjunction with the Society for Pediatric Anesthesia (SPA), has taken the lead in developing a core curriculum for fellowship training in congenital cardiac anesthesia. Collaboration with the ACGME and Residency Review Committee (RRC) is ongoing as the subspecialty matures to the point where it becomes a board-certifiable specialty in its own right. As many children with CHD survive to adulthood and develop the adult cardiothoracic disease, the American Heart Association as well as the American College of Cardiology may be able to provide significant input into developing a holistic approach to the care of this complex patient population. A significant proportion will go on to become pregnant, and hence, both the American College of Obstetricians and the Society for Obstetric Anesthesia and Perinatology will need to contribute to the development of a curriculum.

Conclusion

Developing durable new curricula will be challenging in the highly specialized area of congenital cardiac anesthesia. The use of a systematic approach to its development will facilitate efficient teaching and learning in this complex discipline. It is important to develop programs that give faculty members the necessary skills to develop curricula and that provide mentoring. Collaboration with ACGME for the development of the program requirements and the Milestones development program is ongoing. Finally, the challenge of transitioning trainees from fellow (learner) to the faculty member (provider and teacher) in congenital cardiac anesthesia will continue. The trainees should be encouraged to create a learning portfolio, preferably web-based, that is a record of participation and achievement, career goals and professional development, physical evidence, and reflective writing.

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Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

6 DiNardo JA, Andropoulos DB, Baum VC. Special article: a proposal for training in pediatric cardiac anesthesia. Anesth Analg 2010;110:1121–5.
Despite a relatively universally applicable knowledge base and skill set, training and experience in pediatric cardiac anesthesia in currently organized basic anesthesia and adult cardiothoracic anesthesia fellowship programs are very limited and not uniformly available. The authors present a schema, developed by a working group of the CCAS, for training in pediatric cardiac anesthesia that should be considered by pediatric cardiac anesthesia educators internationally as a template to be modified as necessary.

8 Nasr VG, Guzzetta NA, Miller-Hance WC, et al. Consensus statement by the congenital cardiac anesthesia society: milestones for the pediatric cardiac anesthesia fellowship. Anesth Analg 2018;126(1):198–207.
Training in pediatric cardiac anesthesia is a 12-months fellowship with 18 dedicated milestones based on the six core competencies of the ACGME.

9 Kern DE, Thomas PA, Hughes MT. Curriculum Development for Medical Education: A Six-Step Approach, 2nd edn. Baltimore, MD: The Johns Hopkins University Press, 2009.
This is an excellent resource published by the faculty at Johns Hopkins University, discussing the different steps involved in new curriculum development. Problem identification and general needs assessment. Targeted needs assessment, goals and objectives, educational strategies, implementation, evaluation and feedback are discussed in detail.

10 Wong A. Review article: teaching, learning, and the pursuit of excellence in anesthesia education. Can J Anesth (2012);59:171–81.
Excellent teaching is considered that which facilitates and maximizes learning. A conceptual framework of learning as a convergence of teacher, learner, assessment, and context is proposed in this article. The contribution of each component to learning is examined in order to enable anesthesia teachers to choose and adapt the most appropriate educational approaches for their particular contexts.

11 Nasr VG, Guzzetta NA, Mossad EB. Fellowship training in pediatric cardiac anesthesia: history, maturation and current status. J Cardiothorac Vasc Anesth 2019;33(7):1828–34.
A comprehensive history and review of pediatric cardiac anesthesia training in the United States.

12 Lorello GR, Cook DA, Johnson RL, Brydges R. Simulation-based training in anaesthesiology: a systematic review and meta-analysis. Br J Anaesth 2014;112:231–45.
Using meta-analysis and critical narrative analysis, the authors synthesized the evidence for the effectiveness of simulation-based anaesthesiology training. Their critical analysis showed inconsistency in the measurement of non-technical skills and consistency in the (ineffective) design of debriefing. Simulation in anaesthesiology appears to be more effective than no intervention (except for patient outcomes) and non-inferior to non-simulation instruction.

16 Cook DA. Twelve tips for evaluating educational programs. Med Teacher 2010;32:296–301.
This article helps educators to evaluate an educational program to determine its merit or worth. The two most important questions in any evaluation are, 'Whose opinion matters?' and 'What would really be meaningful to them?'.

17 Ebert TJ, Fox CA. Competency-based education in anesthesiology: history and challenges. Anesthesiology 2014;120:24–31.
The Accreditation Council for Graduate Medical Education is transitioning to a competency-based system with milestones to measure progress and define success of residents. Curriculum must be redesigned and assessments will need to be precise and in-depth.

18 Nasca TJ, Philibert I, Brigham T, Flynn TC. The next GME accreditation system – rationale and benefits. New Engl J Med 2012;366:1051–6.
This article discusses the merits and work that need to be done in the creation of the Next Accreditation System (NAS). Key benefits of the NAS include the creation of a national framework for assessment that includes comparison data, reduction in the burden associated with the current process-based accreditation system, the opportunity for residents to learn in innovative programs, and enhanced resident education in quality, patient safety, and the new competencies.

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CHAPTER 3

Quality, Outcomes, and Databases in Congenital Cardiac Anesthesia

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Introduction

Patient safety in the operating room (OR) and beyond has long been a driving force in anesthesia care. Technical innovations such as pulse oximetry and capnography, combined with better trainee and practitioner education have dramatically increased safety for our patients and the quality of our anesthesia care. Additionally, newer medications, technologies, and monitoring modalities continue to advance the field. As a result of these systematic changes, anesthesia-related patient morbidity and mortality have steadily declined across all patient populations. Non-technical attempts to reduce perioperative complications such as perioperative time-outs and checklists have become another major focus of various organizations such as the World Health Organization (WHO) and the Joint Commission, formerly the Joint Commission for the Accreditation of Hospital Organizations (JCAHO).

Efforts to delineate the frequency of complications related to anesthesia in patients undergoing congenital cardiac surgery and procedures in the cardiac catheterization laboratory and elsewhere have been difficult. This is due to the relatively low frequency of this surgery compared with other surgeries on children and the uncommon incidence of anesthesia-related complications today. Busy cardiac anesthesia services at major North American pediatric institutions will each have contact with 2,000–3,000 congenital cardiac patients/year, and the majority of these cases are non-surgical, such as diagnostic and therapeutic catheterizations and radiology procedures. The recognition of the need to systematically quantify and study outcomes in pediatric cardiac surgery, anesthesiology, cardiac critical care, and cardiology has led to the development of a variety of multi-institutional and multinational efforts to systematically document and study this population.

Educational content reviewed by this chapter will include: (i) A discussion of errors and outcomes in surgery and anesthesia, emphasizing communication and teamwork; (ii) A discussion of systems for prospective risk assessment in pediatric cardiac surgery; (iii) An analysis of closed malpractice claims in anesthesia focusing on pediatric cardiac anesthesia, morbidity, and mortality; and (iv) Database initiatives in congenital cardiac anesthesia, surgery, and interventional catheterization.

Errors and outcomes in surgery and anesthesia

The perioperative management of patients with congenital heart disease (CHD) is fraught and there are occasions when even small decision-making errors can have catastrophic outcomes. James Reason has popularly described the "Swiss cheese model" for evaluating patient complications due to

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human errors [1]. For a complication to occur, all the "holes" in the cheese have to line up – that is, there is a sequential failure of various defense mechanisms in place to prevent, recognize, and/or treat unwanted physiologic changes (Figure 3.1). Many "anesthesia" complications are multifactorial in origin, and it can be difficult to assign the relative contributions of different clinical services. For example, failure to successfully separate from cardiopulmonary bypass may be due to issues such as technical difficulty (surgery and perfusion), residual lesions or bleeding (surgery), inotrope management or mistaken infusion pump programming (anesthesia and surgery), ventilator management (anesthesia), or underlying patient physiology such as intractable pulmonary hypertension (patient). These system factors are further exacerbated if there are communication difficulties between the various parties, including surgeons, anesthesiologists, perfusionists, cardiologists, and the pre- and postoperative medical and nursing teams [2].

In a landmark study, de Leval and colleagues investigated the impact of human factors and teams on surgical outcomes in congenital cardiac patients, focusing on the neonatal arterial switch operation (ASO) as the prototype for complex, high-risk surgery [3]. Patient and procedural data were collected on 243 operations performed by 21 cardiac surgeons in the United Kingdom in 16 centers over 18 months. Of these 243 patients, case study data were collected on 173 ASOs by two human factors researchers who followed each case from the time of induction of anesthesia until care was transferred to the intensive care team. The observed adverse events were subsequently divided into major and minor events depending on their impact on the safety of the patient. Analyses determined that, after adjustment for patient factors, the total number of minor and major events per case were both strong predictors of the probability of major morbidity or death or "near-misses" ($P < 0.001$). The authors concluded that minor events go largely unnoticed by the OR team and are therefore left uncompensated. A subsequent examination of the same data suggests that minor events impede the OR team's ability to compensate for future major events [4]. This investigation only included perioperative care and did not begin to address patient care prior to surgery or after handoff to the intensive care team, which would have added even more events into the calculations.

In addition to the organizational factors, pediatric cardiac surgery procedures have a low error tolerance. The Bristol Royal Infirmary Inquiry and the Manitoba Inquiry reports both recognized the importance of human factors and systems research in improving pediatric cardiac surgical outcomes [5, 6]. The report of the Manitoba Pediatric Cardiac Surgery Inquest found that "serious organizational and personnel problems experienced by the Health Sciences Center's Pediatric Cardiac Surgery Program during 1993 and throughout 1994 contributed to the deaths of these children."

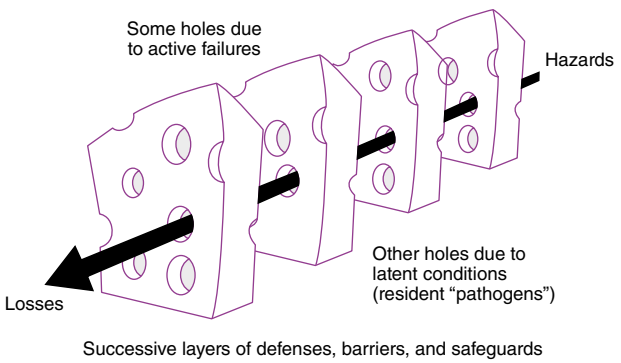


Figure 3.1 The "Swiss cheese" model of accident causation. (Source: Reason [1]. Reproduced with permission of Cambridge University Press.)

Galvan et al. published an observational study on complications in this complex patient population and recorded an average of 1.8 major compensated and nine minor compensated complications per case [7]. These complications were observed during the surgeries but were all recognized and treated by the medical team before injury resulted – all the "holes" in the Swiss cheese did not line up because one or more of the various systems in place to prevent patient injury worked appropriately. Barach et al. reported on a comprehensive process map in which they outlined the multiple steps involved in congenital cardiac anesthetic care and identified the potential sites for safety interventions [8]. They observed 108 open cardiac surgeries and found that communication failures were the most common underlying cause of major events. Examples of the organizational and human factors challenges that Barach et al. observed include:

- Unplanned transfusion of blood products correlated with a breakdown of communication between the anesthesia team, the nurses, and the perfusionist.
- Failure to identify a non-functioning infusion pump was directly related to poor communication between the anesthesia attending physician and the resident who was performing several tasks simultaneously.
- Detection of increased chest tube bleeding was delayed and may have been related to suboptimal communication between residents and the attending physician.

"Near-misses" are important as they are 10–100 times more common than documented adverse events and yet share the same organizational and cognitive sources of error as major adverse events. Determining the frequency and nature of these events is potentially far more important than just looking at system failures resulting in patient injury, a process typically conducted in various quality improvement forums after the events. However, "near miss" analysis is difficult as it requires a trained, independent observer to accompany the patient through the entire care continuum – something that is clearly impractical except in very specific research settings.

Outcome transparency has become a key component of programmatic evaluation. For example, news articles have either disclosed or triggered congenital cardiac surgical program closures possibly related to adverse patient outcomes compared with their cohorts, while other institutions have made the decision to publicly release their pediatric heart surgery outcome data on a regular basis in an attempt to provide the most accurate data possible and fend off any accusations of a program intentionally obscuring their outcomes [9–11]. Although there is currently no mandatory reporting for congenital cardiac surgical or anesthesia programs in the United States, the Society of Thoracic Surgeons (STS) provides "Star" ratings on its website for adult heart surgery outcomes in isolated coronary artery bypass grafting or aortic valve replacement operations [12]. One "Star" programs have risk-adjusted outcomes greater than expected, two

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"Stars" have risk-adjusted outcomes equal to expected, and three "Star" programs have outcomes better than expected based upon the procedure being performed and the patient's underlying preoperative risk factors. Attempts to utilize this same "Star" system in the STS Congenital Heart Surgery Database (STS-CHSD) have not been as successful because of a large number of factors relating to appropriate risk adjustments and the wide variety of case types in CHD.

The STS-CHSD has implemented a voluntary public reporting system that the vast majority of participants in the U.S. participate in. The STS-CHSD public site reports 4-year outcomes stratified by age grouping and adjusted for center case-mix and complexity [13]. In Great Britain, congenital cardiac program mortality is reported publicly for all programs through the central cardiac audit database [14]. To date, there has been no similar effort to publish anesthesia morbidity and mortality, both because it is so infrequent and because of the absence of a national clearing house and the lack of risk adjustment.

KEY POINTS: ERRORS AND OUTCOMES IN SURGERY AND ANESTHESIA

- Reason's Swiss cheese model has widely been cited in explaining patient complications in complex systems.
- The total number of minor and major adverse events during complex congenital heart surgery were strong predictors of morbidity and mortality in de Leval's study.
- "Near-miss" events are 10–100 times more common than adverse events yet they share the same sources of error.

The six "Cs": communication and teamwork

In complex environments like pediatric cardiac ORs or catheterization laboratories, errors cannot entirely be avoided. In his publication, *Normal Accidents*: *Living With High-risk Technologies*, Perrow has postulated that even the best teams cannot eliminate every error [15]. What they can achieve at best is to prolong the time interval between errors. Therefore, it is of great importance for successful hospitals to create a culture of safety similar to the culture that the aviation industry promulgated to minimize the risk of human errors. More than a decade was required before hospitals were able to embed the concepts of checklists, team time-outs and sign in/sign out procedures as components of daily safety procedures. In commercial aviation, one must realize that computers in modern airplanes have taken over the human function of checking lists. These computers are checking the lists themselves automatically because analysis of the human practice of using a checklist a hundred times reveals that this is a source of error in itself. The effort in the aviation industry now is focused more on team performance, simulation, and reducing errors due to hierarchy and authority issues. The six "Cs" – Communication, Cooperation, Coordination, Cognition (simulation and cross-training), Conflict (managing disruptive behavior), and Coaching (team-training) – are the key goals for successful working interdisciplinary teams. A comprehensive summary of this topic is presented by Wahr et al. [16].

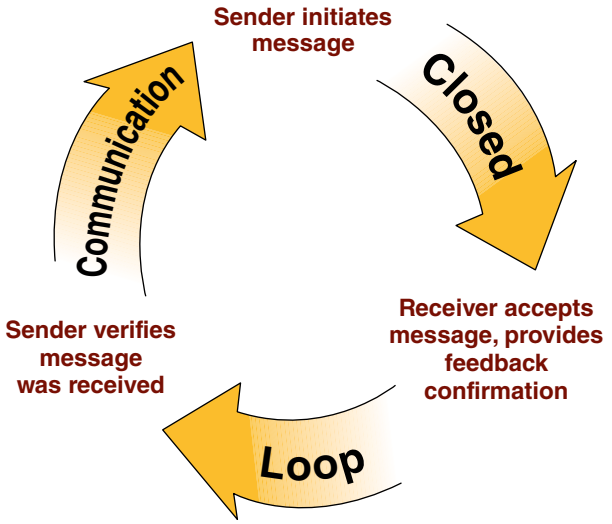


Figure 3.2 Closed-loop communication. (Source: Agency for Healthcare Research and Quality [18].)

The Joint Commission and WHO have both advocated instituting a time-out system prior to procedures to minimize the risk of preventable complications such as wrong-site surgery and failure to administer antibiotics in a timely manner [17]. In addition, "closed-loop" communication has been encouraged to minimize system errors (Figure 3.2) [18]. This particular technique is very helpful in the OR environment, where there can be a wide variety of distractions from background noise, music, cellular telephones, computers, monitors, conversations, and alarms. Shaw and colleagues reviewed much of this literature in their chapter, "Operating room safety, communication and teamwork" in *Gregory's Pediatric Anesthesia* [19]. There are a variety of additional techniques to maximize communication in the OR (or any other procedural location) as well as documenting the flow patterns that may lead to adverse events [17].

KEY POINTS: COMMUNICATION AND TEAMWORK

- Six Cs: Communication, Cooperation, Coordination, Cognition, Conflict management, and Coaching are key goals for interdisciplinary teams.
- Checklists and timeout procedures are now accepted as mandatory components of complex systems such as congenital cardiac surgery.
- Closed-loop communication is an accepted strategy to minimize system errors.

Databases in pediatric cardiac surgery and anesthesiology

Pediatric and congenital cardiac care databases are among the most commonly utilized multicenter areas of study and are in place worldwide in surgery, cardiology, anesthesia,

critical care medicine, hospital-based care, outpatient care, echocardiography, and more [20]. These take the form of either clinical datasets, administrative datasets, or a combination of the two. Many, if not most, of the databases have settled upon a universal set of terms to define the spectrum of congenital heart defects and repairs, the International Paediatric and Congenital Cardiac Code (IPCCC) [21]. The IPCCC has been widely adopted and is now incorporated into the World Health Organization's International Classification of Diseases (ICD), version 11 [22].

In order to better quantify both the incidence of adverse events and the outcomes of surgical procedures, the Society of Thoracic Surgeons' database committee established a nationwide (and now international) voluntary and anonymized registry of congenital cardiac cases and outcomes in the 1990s [23]. This includes almost every congenital cardiac center in the United States and three in Canada. As of the Spring 2019 report, the STS Congenital Heart Surgery Database (STS-CHSD) held information on over 515,659 patient surgical procedures. The European Association for Cardio-Thoracic Surgery (EACTS) has developed a transnational system for congenital cardiac surgery throughout the European continent and the UK. The EACTS utilizes a shared nomenclature for both lesions and complications with the STS that allows pooling of the two datasets to create an even larger picture of worldwide congenital cardiac surgery and outcomes. Other databases in pediatric cardiac surgery worldwide either use the common STS-EACTS nomenclature or similar tools.

The STS-CHSD serves as an important resource for determining United States outcomes on a given congenital cardiac lesion and benchmarks by which individual hospitals and surgeons can compare their results against aggregate results on a lesion-by-lesion, complexity, risk, and age-adjusted basis. Both public and private payers have begun to incorporate these data in evaluating programs. The state of Florida, for example, has mandated participation in this type of database as a requirement for participation in state-run insurance programs such as Medicaid [24]. In New York and Pennsylvania states, the Departments of Health publish outcomes data on every program in their respective states, including whether they fall above or below 95% confidence intervals for expected outcomes after risk adjustment [25]. The private health insurer, United Healthcare, has established "Centers of Excellence" to facilitate referrals within their systems and to maximize their patient outcomes and satisfaction while minimizing the added expense of complications [26, 27]. Demonstration of superior outcomes through benchmarking is one element of the requirements for consideration as a preferred referral center, and the popular US News and World Report Hospital and Specialty annual rankings include database participation and benchmarking in their ranking algorithm [28].

Other important efforts that have come out of the STS-CHSD include working groups that have established the consensus guidelines for defining lesion nomenclature, morbidity, and mortality [29]. All of these efforts have been coordinated internationally with other groups such as the EACTS to allow the free flow of comparative data across national boundaries.

Unlike many countries around the world that utilize a national insurance program and patient registry, the U.S. has not developed a patient identification system that accurately allows tracking of an individual throughout their lifetime and across both state and hospital boundaries. Utilization of something like a Social Security number is impractical due to privacy restrictions and, in the case of the Social Security number, availability at the time of admission, particularly for newborns or for international patients being treated within the United States. At this time, efforts to link the various congenital cardiac surgical and non-surgical databases are relatively limited and rely upon post-hoc linkage of various unique identifiers such as date and place of birth, patient gender at birth, and maternal name. Cardiac Networks United is a consortium of various specialty groups attempting to bridge this gap but its functionality is currently limited by the absence of surgical data from the STS-CHSD [30].

Denmark might serve as a role model because the combined health registers with social registers on an individual level by a unique personal identification number called CPR which is used in all Danish national registers. In 2009, they established The National Centre for Register-based Research [31]. This institution set up a register database in 2010 combining all available registers in Denmark open to researchers. Up to now, the database contains a detailed description of over 45 Danish registries [32].

One well-recognized weakness of single-site reporting systems is that a patient undergoing a procedure at one institution is completely separated from the same individual being cared for at a different institution subsequently, a circumstance which happens frequently with congenital heart care. In the case of an adverse event, the receiving facility becomes the center that reports the morbidity in their statistics, while the initial treating institution may not necessarily report the event. The STS-CHSD is attempting to address this flaw by extending the mandatory follow-up period from 30 days to 1-year post-procedure and through changes in the data collection form which reflect transfers and "salvage" care.

The Congenital Cardiac Anesthesia Society (CCAS) was incorporated in 2005 and one of its first initiatives was to approach the STS about developing anesthesia information to be included in the STS dataset [33]. The first iteration of this collaboration went "live" in January 2010 and has been updated regularly since then. The CCAS work with the STS subsequently served as a model for the Society of Cardiovascular Anesthesiologists (SCA) Adult Cardiothoracic Anesthesia Database, which is now working in conjunction with the appropriate STS dataset. The adult SCA database that began entering patient data in 2013 tends to focus more on patient diagnostic and therapeutic elements rather than outcomes or adverse events [34]. The CCAS is now working with the American College of Cardiology's Improving Pediatric and Adult Congenital Treatment (IMPACT) registry, which collects information about pediatric interventional cardiology and electrophysiology procedures, to include an expanded number of data elements relative to anesthesia including anesthesia type and anesthesia-related adverse events in its next update.

A major benefit of utilizing an annual data submission process across multiple institutions is that it allows for a more contemporaneous examination of patient outcomes. Publications from two centers with a long history of anesthesia data collection, the Boston Children's Hospital and the Mayo Clinic, illustrate the difficulties with single-center record-keeping [35, 36]. Their data, critically important as it is, represents time periods ranging from 6 years (Boston Children's Hospital) to 17 years (Mayo Clinic). During these time spans multiple factors may shift that significantly alter

patient outcomes and potential complications. For example, personnel changes and experience (physician, nursing, and ancillary staff), surgical technique modifications, pharmacology, technical advances with better monitoring and equipment, and more sophisticated complication detection and tracking all impact patient outcome statistics.

In examining low-frequency events, the only way in which to accurately estimate their occurrence is to investigate large numbers of patients. No single center can provide sufficient patients as a denominator in a relatively short period of time; therefore, it is necessary to either lengthen the epoch studied (with the weaknesses mentioned earlier) or increase the denominator by expanding the patient base by making the data multi-institutional, recognizing that by increasing the sites participating one may decrease the relative consistency and accuracy of the data collected. One goal of the STS–CCAS collaboration is specifically to do the latter.

KEY POINTS: DATABASES IN PEDIATRIC CARDIAC SURGERY AND ANESTHESIOLOGY

- The STS Congenital Heart Surgery Database (CHSD) is the most widespread multi-institutional effort to gather data on practice and outcomes in congenital heart surgery.
- The EACTS has also developed a similar database for congenital heart surgery.
- Cardiac anesthesia databases have been initiated by the CCAS and the SCA, appended to the surgical databases.

Prospective risk assessment in pediatric cardiac surgery and cardiology

It is intuitive that different pediatric cardiac surgical procedures will have radically different long-term outcomes related to the underlying severity of the defect(s) (including *in-utero* effects on blood flow patterns), the complexity of the operative repair, and the co-morbidities found in a given patient as well as non-defect related elements such as patient socio-economic factors, racial disparities, parental education levels and insurance status [37].

In order to best estimate these potential outcomes, initial efforts were made at developing risk categories based upon "best guess" techniques in which groups of cardiac surgeons and cardiologists sat down in a room and assigned each individual operative procedure to a risk category pool based upon their collective years of experience. The most widely adopted categorization schema utilizing this technique is the Risk Adjustment for Congenital Heart Surgery (RACHS-1) scoring system developed by Jenkins and colleagues [38, 39]. The Aristotle Basic Complexity (ABC) score is another attempt at preoperative risk assessment utilizing expert consensus based upon values being assigned to three components: the potential for perioperative mortality, the potential for perioperative morbidity, and the technical difficulty of the proposed repair [40]. The ABC system expanded the number of procedures evaluated, as compared with the RACHS-1 system, but the RACHS-1 appears to better discriminate at predicting mortality when the two are compared against each other [41]. The weakness of both these systems is that they are based upon a consensus estimation of experts in the field. The STS-CHSD, in conjunction with the EACTS, subsequently developed a risk model developed from empirical outcome data from two large databases, the Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) mortality score. The initial STAT mortality scores were modeled utilizing over 70,000 records from the two societies and the pediatric cardiac surgical procedures were divided into five levels of mortality categories ("strata"); however, these are based upon the observed outcomes rather than *a priori* assignment by expert opinion and this process was then validated by comparison to a larger sample set of over 111,000 pediatric cardiac surgical cases in both the STS and EACTS registries [42]. This STAT mortality score has recently been updated, incorporating more procedures and frequent combination procedures and updated based upon more current outcome data solely from the STS-CHSD [43]. Each STAT mortality category was created so that the inter-category differences were sufficient to warrant assignment to either a lesser or a greater score category. Table 3.1 contains a listing of the newest STAT-assigned procedures or procedure combinations and their respective categories. The STAT, RACHS-1, and ABC scores are all based upon in-hospital mortality rates and do not fully account for either in-hospital morbidity or out-of-hospital mortality, such as inter-stage deaths that occur more than 30 days after the procedure or either hospital discharge, whichever is later. Another major component that is not fully accounted for in these systems is preoperative morbidity, such as prematurity, genetic abnormalities, or co-existing diseases. Post-operative mortality after hospital discharge, and residual surgical lesions are also not captured. Work is progressing on each of these issues as they relate to patient outcomes. Concerns within the STS-CHSD related to differences in surgical outcomes based upon the patient's underlying diagnosis have also led to ongoing research examining the impact of diagnosis-procedural (D-P) combinations. For example, the modified Blalock-Taussig shunt palliative procedure may be performed for a very heterogeneous group of underlying anatomic diagnoses with inadequate or abnormal pulmonary artery blood flow. Ongoing research efforts using complex large machine-learning models are currently underway to determine if these D-P combinations impact patient mortality estimates differently than a purely procedure-based model such as the current STS-CHSD utilizes. This work has now shown that except for helping discriminate between very high risk procedures, the addition of diagnosis to the procedure did provide additional benefit in predicting post-operative mortality [44, 45].

Pasquali et al. have drawn extensively from work done in adult cardiovascular surgery to determine the relevance of "failure to resuscitate" (FTR) as a marker for programmatic quality [46]. The authors start with the hypothesis that complications and morbidity will always occur in any complex system such as the surgical repair of congenital heart defects. A single-site retrospective analysis by Agarwal and colleagues found an incidence of identified adverse events of 43% (126 of 325 patients); this was in a retrospective chart review, not in the type of prospective observational study performed years earlier by de Laval and Barach, which might identify more subtle minor events that occur without being recorded [3, 8, 47]. What distinguishes high-performing programs from lesser-performing ones is not the incidence of adverse events *per se*, but the response to them.

Table 3.1 Society of Thoracic Surgeons – European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) Mortality Score categories

STS expected hospital discharge mortality rate (95% confidence interval)				
Mortality category 1 (0.20–1.33%)	**Mortality category 2 (1.43–2.94%)**	**Mortality category 3 (3.01–6.82%)**	**Mortality category 4 (6.88–13.00%)**	**Mortality category 5 (13.45–38.68%)**
Aortic stenosis, subvalvar	Valvuloplasty, mitral	Coarctation + VSD repair	Unifocalization, bilateral complete	ASO + VSD + aortic arch repair
Valve replacement, pulmonic	Valvuloplasty, Aortic – converted to AVR	Pulmonary artery aneurysm repair	TAPVC repair	Unifocalization, bilateral, incomplete
ASD repair, patch +PAPVC	Atrial fenestration closure	MAPCA unifocalization	ASD + aortic arch + VSD	Shunt, Potts' type
ASD repair, Patch	Arrhythmia surgery, ventricular	Systemic venous stenosis repair	Ross–Konno	Valve replacement, common AV valve
AVC repair, intermediate	Annular enlargement procedure	ASD partial closure	Fontan revision or conversion	Truncus + interrupted aortic arch
ASD repair, primary	PA reconstruction, Branch, Central	ccTGA, VSD closure	Ross–Konno, valvuloplasty converted to aortic valve replacement	Norwood
Conduit reoperation	Valve closure, semilunar	DORV repair	Senning	Unifocalization MAPCAs + Central shunt
PAPVC, baffle (Warren)	Glenn (unidirectional)	MAPCA occlusion	TOF – AVC repair	Hybrid stage 1
AAOCA repair	Glenn (bidirectional)	Aortic arch repair	Valvuloplasty converted to a replacement, common AV valve	ASD partial closure + pulmonary venous repair
DCRV repair	PA band adjustment	Hepatic vein to azygous graft	Valve closure, tricuspid	Hybrid stage 1 + bilateral PA bands + PDA stent
Vascular ring repair	Arterial switch + aortic arch repair	TOF, RV-PA conduit	Glenn + AV valvuloplasty	Ebstein's repair + PDA closure
TOF, ventriculotomy, nontransannular	Shunt, ligation and takedown	Fontan, atrio-pulmonary	PDA + modified BT shunt	Shunt, modified BT + DKS
Fontan, lateral tunnel, fenestrated	ASD + TOF repair, no ventriculotomy	ASD repair, common atrium	Yasui	Ross–Konno + valve replacement, mitral
PFO, primary	Mitral stenosis, supravalvar ring	Hybrid approach, transcardiac device placement	Aortic root replacement, homograft	Valvuloplasty, tricuspid + Norwood + RV-PA conduit
VSD repair, patch	Conduit placement, RV to PA	Mustard procedure	VSD + ASD + PAPVC	PA Banding + valvuloplasty, common AV valve
PAPVC repair	PAPVC, Scimitar	Valvuloplasty converted to a replacement, Pulmonic	Cardiac tumor resection	Hybrid stage 1 + bilateral PA bands
TOF, no ventriculotomy	Coronary artery fistula ligation	Aortic root translocation	Pulmonary venous stenosis repair	TAPVC + shunt, systemic – pulmonic
Aortopexy	Anomalous coronary from the pulmonary artery	Coronary artery bypass	PA reconstruction (central) + modified BT shunt	TAPVC + shunt, systemic – pulmonic + PDA closure
Valvuloplasty, pulmonic	VSD creation/enlargement	Pericardial drainage procedure	Valvuloplasty converted to a replacement, tricuspid valve	
Ross procedure	LV to aorta tunnel repair	Valve replacement, aortic, homograft	Central shunt	
AVC repair, partial	PDA closure, surgical	TOF, ventriculotomy, transannular patch + vascular ring repair	Shunt, reoperation	
Pacemaker procedure	Pulmonary atresia-VSD repair s/p unifocalization	Transplant, heart	PA banding	
VSD repair, primary	ASD repair, device	Valve replacement, mitral	Central shunt, Mee type	

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Aortic root replacement, bioprosthetic	Bilateral bidirectional Glenn	Valvuloplasty converted to replacement, mitral	PA reconstruction + heart transplant
RVOT procedure	ASD + PV replacement	Interrupted aortic arch repair	Transplant, lungs
Valve replacement, Aortic	ASD + PAPVC	Valvuloplasty, aortic + valvuloplasty, mitral	Aortic dissection repair
Valvuloplasty, Tricuspid	VSD repair + conduit	VSD patch + AVC repair	Truncus arteriosus repair
AS repair, subvalvar with myectomy	PA reconstruction, Branch, peripheral	Coarctation, subclavian flap	ASD + pulmonary atresia/VSD repair, including TOF pulm atresia
Valvuloplasty, aortic	VSD multiple, repair	Ventricular septation	Unifocalization + conduit placement
Pulmonary sling repair	Glenn + PA plasty	Ventricular septum fenestration	TOF – absent PV
Sinus of Valsalva aneurysm repair	VSD + valve replacement, pulmonic	REV	HLHS biventricular repair
PA reconstruction, main trunk	Conduit placement, Ventricle to aorta	Pulmonary embolectomy, chronic	Conduit, RV – PA + aortic root replacement
Valvuloplasty, Truncal valve	Removal of transcatheter delivered device from heart	Valve replacement, Tricuspid	AVC repair, complete + coarctation end-end
Rastelli procedure	Batista procedure	Arterial switch + VSD	RV – PA conduit + PDA closure
Explantation of pacemaker	Valvuloplasty, common AVV	Unifocalization, MAPCAs	Hybrid stage 2 + aortic arch repair
Coarctation repair, end-to-end	PA debanding	Fontan, external, hepatic veins to PA, fenestrated	Pulmonary artery sling + tracheal repair
Aortic aneurysm repair	Anomalous systemic venous connection	Tricuspid valve excision without replacement	
Hemi-Fontan	VSD repair, device	Hybrid stage 2 without aortic arch repair	
ASD, primary + VSD repair, patch	Arterial switch operation	Fontan, external conduit, fenestrated + pacemaker	
Aortic root replacement, valve sparing	Valve excision, pulmonary	Fontan, external, hepatic veins to PA, nonfenestrated	
Coarctation repair, patch	Acute pulmonary embolectomy	Hybrid, transcardiac	
Valve replacement, Aortic, mechanical	Ligation, pulmonary artery	Damus-Kaye-Stansel	
1 1/2 Ventricular repair	Sternotomy wound drainage	ccTGA, atrial switch + Rastelli	
AICD Implantation	VSD – MAPCA, single stage repair	Shunt, modified BT	
Coarctation repair, interposition graft	Atrial baffle procedure	AVC + vascular Ring	
Arrhythmia surgery	Pericardiectomy		
Fontan, external conduit, nonfenestrated	Aortic stenosis repair, supravalvar		

(*Continued*)

Table 3.1 (Continued)

STS expected hospital discharge mortality rate (95% confidence interval)				
Mortality category 1 (0.20–1.33%)	**Mortality category 2 (1.43–2.94%)**	**Mortality category 3 (3.01–6.82%)**	**Mortality category 4 (6.88–13.00%)**	**Mortality category 5 (13.45–38.68%)**
Aneurysm repair, right ventricle	ccTGA, double switch repair			
Pacemaker implantation, permanent	cc TGA, LV to PA conduit			
Fontan + AV Valve repair	DOLV repair			
Hemitruncus repair	Pulmonary AV fistula repair			
Fontan, external conduit, fenestrated	Conduit reoperation + AVR			
Kawashima operation	Pulmonary atresia – VSD repair			
Cor triatratum repair	Fontan, intra/extracardiac repair, nonfenestrated			
AP window repair	Cardiac tumor resection			
Fontan, intra/extracardiac, fenestrated	Aortic arch + VSD repair			
	Valve replacement, truncal			
	Fontan takedown			
	Glenn takedown			
	Vascular stent removal			
	ASD creation/enlargement			
	Konno procedure			
	Aneurysm repair, LV			
	Ebstein's repair			
	Conduit, LV to PA			
	Atrial baffle, Mustard or Senning			
	Pulm valve replacement + pacing explant			
	Pulmonary atresia – VSD MAPCA s/p unifocalization			
	VSD + PAPVC			

AICD, automated internal cardiac defibrillator; AP, aortopulmonary; ASD, atrial septal defect; ASO, arterial switch operation; AVC, atrioventricular canal; AVR, aortic valve replacement; ccTGA, congenitally corrected transposition of the great arteries; DCRV, double-chambered right ventricle; DKS, Damus–Kaye–Stansel; DOLV, double outlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; LV, left ventricle; MAPCAs, major aortopulmonary collateral arteries; PA, pulmonary artery; PAPVC, partial anomalous pulmonary venous connection; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PVR, pulmonary valve replacement; REV, reparation a l'étage ventriculaire (REV procedure); RV, right ventricle; RVOT, right ventricular outflow tract; TAPVC, total anomalous pulmonary venous connection; TCPC, total cavopulmonary connection; TOF, tetralogy of Fallot; TVR, tricuspid valve replacement; VSD, ventricular septal defect.
Source: Adapted from Jacobs et al. [43].

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Interventional cardiologists have also addressed predictive outcomes analysis. In 2007 the Congenital Cardiac Catheterization Project on Outcomes (C3PO) registry was created to establish standardized and comparable metrics across 15 pediatric cardiac catheterization laboratories, utilizing an internet-based tool on all cardiac catheterization cases [48]. *Post hoc* analyses utilizing multivariate modeling then determined four discrete procedural risk categories based upon the age of the patient and the type of procedure being performed (diagnostic, valvuloplasty, device or coil closure, angioplasty, stent placement, stent redilation, and others). Adverse events were categorized on a scale of 1–5, with 1 being no adverse event noted, and 5 catastrophic (i.e. resulting in death or emergent surgical intervention to prevent death). The risk scoring method was called the Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM). The purpose of the C3PO and CHARM project is to allow for appropriate risk adjustments to be made when comparing outcomes at a given center with expected outcomes for their specific patient population. Over a 2-year-period approximately 10,000 cases were analyzed to develop predictors of adverse events which included hemodynamic parameters such as cardiac index, right ventricular pressures, and the right ventricular to systemic pressure ratio [49]. The C3PO-QI database evolved from this endeavor in 2013 to address quality improvement issues in the catheterization laboratory. This prospective data registry includes over 13,000 cases and aims to improve standards of care in pediatric cath labs, including initiatives on radiation exposure [50]. This is a critical part of the quality improvement process that must occur at every institution.

Similarly, the IMPACT Registry was created in 2011 with the aim of creating risk stratification among common pediatric cath lab cases, and tracking outcomes comparing high versus low performing centers [51]. In order to achieve this, IMPACT created learning collaboration with the National Pediatric Cardiology-Quality Improvement Collaborative (NPC-QIC). The NPC-QIC's focus is to reduce themortality rate and improve the quality of life for small children with hypoplastic left heart syndrome in the interstage period between the Norwood and Glenn Procedures. The key drivers of this quality improvement initiative extend beyond the pediatric cath lab and include factors such as nutritional status, discharge coordination, and home medical surveillance. This quality improvement collaborative was able to demonstrate a 44% reduction in interstage mortality amongst the participating centers.

KEY POINTS: PROSPECTIVE RISK ASSESSMENT IN PEDIATRIC CARDIAC SURGERY AND CARDIOLOGY

- The STAT score is a risk model developed from empiric outcome data and is the most accurate method for estimating mortality risk preoperatively.
- The CHARM and IMPACT projects estimate the risk of adverse outcomes according to the complexity of the interventional cardiac catheterization procedure.

Closed claims analysis in anesthesia

The American Society of Anesthesiologists has sponsored multiple investigations using a "closed claims" analysis method to identify areas of concern for anesthesiologists, including claims for death and brain injury, central venous line injuries, nerve injury, and airway injury [52–56]. These reports have not generally examined the effects of age or type of surgery and do not have a denominator that is needed to determine the incidence of injury. Jimenez et al. used the closed claims data to investigate pediatric anesthesia liability and segregated the data by type of surgery [57]. This report found that thoracic and cardiac surgeries accounted for slightly less than 10% of all claims that were settled. This figure probably represents a disproportionately high number because of the relatively small number of thoracic and cardiac surgeries compared with all surgeries performed on pediatric patients. In general, malpractice data are a very insensitive tool for determining the incidence or causality of complications, as many different factors apart from medical error determine whether or not a claim is initiated or settled. The denominator of pediatric patients undergoing surgical and diagnostic procedures with anesthesia in the United States is not measurable with any accuracy due to the lack of a central reporting mechanism. Examining the caseload at children's hospitals is insufficient because many procedures are performed in mixed adult–pediatric general hospitals, ambulatory surgical centers, or physicians' offices. In addition, many adult congenital heart procedures are performed by adult cardiac surgeons and cardiologists and never entered into any congenital databases. For example, bicuspid aortic valve stenosis is very frequently treated in adult facilities but is widely acknowledged to be a congenital structural defect rather than an acquired disease, particularly when presenting at younger ages compared to acquired aortic valvular disease.

Pediatric and congenital cardiac anesthesia morbidity and mortality

Numerous anesthesia-related manuscripts concerning cardiac arrest in children have been published, some of which focused on children with CHD, with others focusing on children undergoing all types of surgical and non-surgical procedures [35, 36, 58, 59]. The pediatric perioperative cardiac arrest (POCA) registry was a multi-institutional effort in which participants anonymously reported all episodes of cardiac arrest in children aged 18 and younger that resulted in chest compressions or death at the time of surgery or within 24 hours. This project was begun in 1994 and data collection and analysis continued through 2004, at which time further data collection was put on hold. Subsequent examination of the detailed data forms allowed the investigators to assess the relative contribution of anesthesia to the cardiac arrest or death. A subsequent publication from the POCA group was a follow-up to their original publication in 2000 and focused the analysis on arrests in patients with heart disease [60, 61]. The authors reported that cardiac arrests in these patients were more likely to be in unrepaired patients

(59%) or palliated patients (26%) than in patients with repaired cardiac lesions (15%). Finally, in 2010, Ramamoorthy et al. re-examined the POCA data, specifically assessing children with congenital heart defects [62]. Overall, they found that of the 373 anesthesia-related cardiac arrests, 127 (34%) patients had congenital or acquired heart disease – a number, not surprisingly, far out of proportion to the incidence of heart disease in the pediatric population (0.8%). Patients with single ventricle physiology were those most likely to suffer a cardiac arrest, while those with aortic stenosis and cardiomyopathy were associated with the highest mortality rates.

Building on the scope of the POCA Registry, Wake Up Safe (WUS) was established in 2008 with the aim of improving perioperative processes and care for children receiving general anesthesia [63]. An initiative started by the Society for Pediatric Anesthesia (SPA), the mission of WUS is to provide ongoing monitoring of very rare adverse events under general anesthesia across multiple institutions, and to use these data to uncover ways to prevent them from recurring. Centers participating in WUS have grown from the initial 19 participating pediatric hospitals in the United States to 34 as of the time of this writing [64]. In order to study these events, WUS created an organized multicenter detailed voluntary registry to record serious adverse events during the perioperative period [65]. Data collected by WUS not only consist of cardiac arrest events like POCA but also includes "near miss" events such as acute lung injury, musculoskeletal injury, spinal cord injury, or surgery on the wrong patient/site. Because of the way in which the WUS initiative is structured, it should be possible to determine the incidence of these events and not just record their existence. Limitations to this database include reporting bias, as this is a voluntary non-audited registry and the membership of a proportionately small number of US academic institutions. WUS does not reflect the events that may occur at ambulatory surgery centers, private offices (e.g. dental operatories), and general community hospitals; locations where the majority of pediatric anesthetics are provided in the United States.

Since the WUS project began, statements have been published on the WUS website concerning hyperkalemia, preventing wrong-site procedures, and decreasing the risks of intravenous medication errors. In 2014, WUS published their first database analysis of adverse events from 2008 to 2013: of 736,365 pediatric anesthetics of all subspecialties in the database, there was a serious adverse event rate of 1.4/1,000 anesthetics (0.05%), with respiratory events most common (254 of 740) and cardiac arrest the next most frequent (241) [65]. Five years later, the event data from the 19 original institutions was examined along with a root cause analysis on the anesthetics performed from 2010 to 2015 [64]. Compared to the previous study, 0.104% of the 1,964,211 children receiving an anesthetic experienced an adverse event. Consistent with most studies, the incidence of adverse events was higher in neonates/infants and those with ASA status of IV or higher. The most commonly reported adverse events in this study were cardiac (31.6% total events, 3.3/10,000), respiratory (29.2% of total events, 3/10,000), medication (16.9% of total events, 1.8/10, 000), and perioperative death (8.5% of total events, 0.9/10, 000). However, after root cause analysis, events judged to be primarily caused by anesthesia demonstrated medication events as the most common (31.9%), followed by respiratory (24.1%), and finally cardiac arrest (18.5%). The findings of this study suggest that QI efforts aimed at the reduction of medication events would be the most impactful.

The investigators at Boston Children's Hospital have been collecting anesthetic data on their own patients since January 2000, both for internal quality and for state reporting requirements in Massachusetts. The publication of this data through December 31, 2005 from their cardiac ORs represents a significant single-site effort to determine contemporary complications specific to pediatric cardiac anesthesia-related morbidity [35]. One of the difficulties associated with determining causality in this patient population is the interdependent nature of anesthesia, surgery, and patient physiology. The authors examined each incident with a panel of three pediatric cardiac anesthesiologists, with a subsequent review by a pediatric cardiac surgeon, before assigning causality. Boston Children's Hospital reported that in their series of 5,213 cardiac surgical patients from 2000 to 2005, there were 41 cardiac arrests in 40 patients for an overall frequency of 0.79%, with anesthesia playing a significant role in 11 of the 41 cases; in other words, 21.1 cardiac arrests/10,000 anesthetics were reported. This compares with their previously reported anesthesia-related incidence of 2.7 cardiac arrests or death/10,000 anesthetics in all pediatric patients during roughly the same period [66].

In 2013, the investigators from Boston Children's Hospital again reviewed their institution's database to examine the incidence of cardiac arrest in children with CHD undergoing cardiac catheterization and to describe potential risk factors for anesthesia [58]. In total, 7,289 catheterization procedures were performed between January 1, 2004 and December 31, 2009, and were classified as either a biopsy (19%), diagnostic (23%), or interventional catheterization (58%) [58]. Seventy procedures were associated with a cardiac arrest, with a reported frequency of 0.96/100 cardiac catheterizations. The authors acknowledge that although the frequency of arrest is higher than other multi-institutional reports, it is comparable to the results of their prior study on the incidence of arrest in the cardiac OR. The incidence of cardiac arrest in the population studied was found to be statistically significantly higher for children undergoing interventional procedures and those who were younger at the time of the procedure ($P < 0.001$). These authors concluded that these high-risk patients should be managed by an anesthetic team familiar with the pathophysiology, cases, environment, and perioperative staff, in order to facilitate communication and prompt resuscitation should the need arise. There also appeared to be an overall decline in the incidence of cardiac arrest when sedation and anesthesia were provided more routinely by a dedicated pediatric cardiovascular anesthesia team in the latter half of the data collection period.

Another institution with a long history of anesthesia data collection, the Mayo Clinic in Rochester, MN, also reviewed their experience with cardiac arrests in children [36]. A consistent factor in all of these studies is that children with underlying congenital cardiac defects are at a much higher risk of cardiac arrest than children without these defects. The incidence of cardiac arrest at the Mayo Clinic for children during non-cardiac procedures was 2.9/10,000, as compared

with 127/10,000 for children undergoing cardiac procedures, a 30-fold increase in risk. Sub-analysis related to causality, age, and the type of surgery further stratified their data. Of their 92,881 patients, 4,242 were for cardiac procedures. Within the 54 children who suffered a cardiac arrest or death undergoing a cardiac procedure, age played a significant role, with neonates having the highest risk. Anesthesia was not identified as a causative factor in any of the cardiac surgical arrests or death. At the Royal Children's Hospital, Melbourne, Australia, van der Griend and colleagues examined anesthesia-related mortality in 101,885 anesthetics administered to 56,263 children from January 1, 2003 through August 2008 [59]. They, too, utilized an expert review panel of three senior anesthesiologists, examining the record of every patient who died during this period but who had received an anesthetic in the preceding 30 days. Overall anesthesia-related mortality was found to be 1 in 10,188 cases (0.98/10,000). All 10 deaths where anesthesia was found to be a contributing factor had significant pre-existing conditions, with pulmonary hypertension present in 50%. There were no anesthetic-related morbidities in children without underlying medical problems. Overall mortality was significantly higher in children <30-days old and those with cardiac disease (particularly after 30 days of life).

Recently, a group of collaborators coming from the European Pediatric Anesthesia community started two large Pan-European studies funded by the European Society of Anaesthesiology Clinical Trial Network (ESA CTN) and supported by the European Society for Paediatric Anaesthesia (ESPA) to investigate the incidence of severe critical events in children and neonates undergoing general anesthesia in Europe. The main finding of the Incidence of Severe Critical Events in Paediatric Anesthesia (APRICOT) study was that the incidence of perioperative severe critical events was 5.2% (95% CI 5.0–5.5) with an incidence of respiratory critical events of 3.1% [67]. This was independent of the type of anesthesia administered. In the APRICOT study, 30,784 children from 33 countries, mainly from Europe, were included. Besides the main findings, the study revealed that the standard operating procedures differ enormously within not only the countries but also participating centers. One could observe more than 40 combinations for premedication, at least 100 different methods for anesthesia induction, and more than 40 different types of crystalloid infusions combined with or without glucose. Only 1.6% of anesthetics were cardiac surgery or catheterization, and the incidence of congenital heart disease in the entire group was not specifically reported. Cardiac surgery conferred a relative risk (RR) for cardiac severe critical events of 16.92 (95% CI 13.67–20.93, $p<0.0001$), and cardiac catheterization a RR of 3.20 (95% CI 1.71–5.85, $p<0.0001$). The NEonate and Children AudiT of Anaesthesia PRactice IN Europe (NECTARINE) study was of a similar design but the age group was neonates and infants up to 60 weeks' postmenstrual age in 165 centers in 31 European countries [68]. A total of 6,542 anesthetics were performed; 12.7% of patients had congenital heart disease, which was not specifically analyzed as a risk factor for the entire group. Of 5,200 surgical procedures, 439 (8.4%) were for cardiac surgery, which was the second most common operation after inguinal herniorrhaphy. Cardiac surgery was consistently the highest risk factor for morbidity at 30 days (51.6%, RR 3.08, 95% CI 2.65–3.57, $p<0.01$) and 30- and 90-day mortality (9.45%, RR 2.67, 95% CI 1.61–4.42, $p = 0.002$). The findings of the two large multicenter, Pan-European studies give important information regarding how to set up studies or databases within different countries. Moreover, in an accompanying editorial Lerman pointed out that the multivariate analysis revealed that senior anesthesiologists had 1% fewer critical respiratory events per year of experience [69]. Additionally, the frequency of critical events from centers that reported these events was inversely associated with the number of children anesthetized.

As is evident from the most recent data, even the busiest of programs only infrequently have anesthesia-related cardiac arrests or death because of the low incidence of these events. As a consequence, it is necessary to harvest data over many years to collect any meaningful numbers, during which time major changes in patient management may occur. For example, the initial POCA study attributed many arrests to the use of the anesthetic agent, halothane, a known cardiac depressant [61]. By the time of the follow-up publication 7 years later, halothane had been replaced almost entirely in North America by sevoflurane, an anesthetic agent with significantly less cardiotoxicity at the typically administered doses.

KEY POINTS: PEDIATRIC AND CONGENITAL CARDIAC ANESTHESIA MORBIDITY AND MORTALITY

- The POCA Registry reported that 34% of cardiac arrests under anesthesia had heart disease as a factor.
- The Boston Children's Hospital registry has reported a cardiac arrest rate of 0.79% for cardiac surgery, and 0.96% for cardiac catheterization.
- The Mayo Clinic study reported a 30-fold increase in the risk of cardiac arrest with cardiac surgery vs. non-cardiac surgery in pediatric patients.
- The Royal Children's Hospital study reported that pulmonary hypertension was a factor in 50% of anesthesia-related deaths.
- The APRICOT and NECTARINE studies from Europe reported that cardiac surgery or catheterization was the highest risk factor for critical events, morbidity, or death with relative risk 2.6–16.9 times other procedures.

Congenital Cardiac Anesthesia Society and the Congenital Cardiac Anesthesia Network

The Congenital Cardiac Anesthesia Society was formed in 2005 by representatives drawn from many of the busiest congenital cardiac surgical programs in North America. It is a subsidiary of the Society for Pediatric Anesthesia and its work is closely coordinated with that organization. Membership is open to all individuals providing anesthesia-related care for children with heart defects or an interest in the field and it currently has almost 1,300 members both

from the US and international programs. In addition to educational programs at its conferences and as a sponsor of other educational efforts, a major function of the organization is the development of a data registry linked to the STS-CHSD. In the UK and Ireland, the Congenital Cardiac Anaesthesia Network (CCAN) is an informal organization of pediatric cardiac anesthetists numbering 70–80 physicians, which sponsors an annual meeting for presentation of timely topics and discussion/debate about clinical practices. CCAN also sponsors a mailing list for regular updates.

Joint CCAS–STS database initiative

The Joint CCAS-STS Congenital Cardiac Anesthesia Database is a collaborative project developed over the last decade by multiple parties interested in capturing anesthesia-related information on these high-risk patients. The process by which this project came about is described previously [8]. Anesthesia-related data fields for the database are selected by a database committee of the CCAS in coordination with the existing fields in the STS-CHSD. For an additional fee, STS-CHSD participating centers may elect to submit their anesthetic data to be pooled anonymously with the other participating centers during their annual data harvest.

The interdependent relationship between congenital cardiac surgery and congenital cardiac anesthesia supports the creation of a common database for these subspecialties. Multiple potential benefits are being realized through the development of this joint database:

- Minimization of data entry burden
- Minimization of costs associated with data entry
- Minimization of the cost associated with database maintenance
- Utilization of common nomenclature based on the International Pediatric and Congenital Cardiac Code [70].
- Utilization of common database fields
- Utilization of common database definitions
- Utilization of common database standards
- Development of common strategies to report outcomes
- Development of common quality improvement initiatives.

The Joint CCAS-STS Congenital Cardiac Anesthesia Database began collecting data in January 2010. The data are harvested semi-annually, though the STS is currently moving to a continuous harvest process with semi-annual reporting and analysis. The most recent report from the STS-CHSD was published in 2020 containing data for the 4-year period ending June 30, 2019[71]. Reviewing only cardiac surgery procedures either with or without cardiopulmonary bypass (excluding minor procedures, ECMO or VAD or non-surgical procedures), there were 66,655 cases in the dataset. Of these, 50,633 included bypass and 15,318 were non-bypass cases such as repair of coarctation of the aorta or pacemaker placement. Adverse events were reported overall in 1,653 of the 66,655 (2.5% or else 2.47%) These data were derived from over 60 anesthesia reporting sites.

The STS-CHSD, including the anesthesia component, is updated approximately every 3 years. The most recent update went live on July 1, 2021. The CCAS Database Committee has made several modifications to the data being collected, including multiple additions to the adverse outcome reporting options. The committee has also worked with the STS to consolidate and clarify duplication of data entry items, such as blood transfusion categories, and added additional medication and blood product categories to reflect newer pharmacologic options. The complete data collection forms are available on the STS website, as is information about how to become a participating center [71]. Table 3.2 lists the adverse events being collected by the CCAS–STS-CHSD.

Table 3.2 Congenital Cardiac Anesthesia Society–Society of Thoracic Surgeons Database Adverse Event Fields (as of January 1, 2021)

Event	Definition
None	No anesthesia-related adverse events noted in the perioperative period
Cardiac arrest events	
Cardiac arrest – anesthesia-related	Cardiac arrest requiring CPR during anesthesia care not related to surgical or catheter manipulation
Cardiac arrest – not anesthesia-related	Cardiac arrest requiring CPR during surgical or catheter manipulation
Airway–related events	
Difficult intubation/reintubation	Unplanned difficult intubation or reintubation
Unplanned extubation	Unplanned extubation (except if TEE-related – see below)
Bronchospasm	Wheezing requiring medical intervention other than suctioning
Endotracheal tube malposition	Endotracheal tube needing to be repositioned in ICU on arrival chest X-ray
Stridor/subglottic stenosis	New-onset stridor noted after extubation requiring intervention
Oral/nasal injury – bleeding	Bleeding noted in oropharynx or epistaxis, dental, lip, or nasal injury
Laryngospasm requiring medication	Laryngospasm requiring medical intervention other than positive pressure
Hemoptysis/pulmonary hemorrhage	Bleeding either from the endotracheal tube or postoperative hemoptysis
Respiratory arrest	Need to intervene in airway management in an unplanned way (i.e. converting from the cannula to ETT or LMA to ETT)
Airway injury	Barotrauma/pneumothorax secondary to positive pressure ventilation

(*Continued*)

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Table 3.2 (Continued)

Event	Definition
Medication-related events	
Protamine reaction	Significant reaction to protamine requiring intervention other than slowing administration
Anaphylaxis/anaphylactoid reaction	Suspected anaphylactic/anaphylactoid reaction requiring intervention for either hemodynamic support or respiratory intervention
Medication dosage	Wrong dosage of correct medication
Medication administration	Wrong medication administered
Non-allergic drug reaction	A nonanaphylactic reaction such as "red man" syndrome or hypotension
Malignant hyperthermia	Suspected or confirmed malignant hyperthermia reaction requiring dantrolene
Vascular access events	
Arrhythmia – CVL placement	Arrhythmia therapy needed other than withdrawing wire or catheter
Myocardial injury – CVL placement	Myocardial perforation
Vascular compromise – CVL placement	Extremity ischemia or compromise with CVL placement
Pneumothorax – CVL placement	Pneumothorax during placement of CVL
Vascular access	Inability to obtain desired vascular access within 1 hour of induction anesthesia (PIV/Aline/CVL)
Hematoma requiring relocation of the catheter	Significant hematoma that requires changing the site of desired access
Arterial puncture	Inadvertent arterial puncture during CVL placement
Intravenous/intra-arterial air embolism	Air embolism causing hemodynamic change or ischemia
Arterial line placement – extremity ischemia	Extremity ischemia or compromise with the arterial line placement
Intravenous Infiltration	Peripheral or central IV infiltration
TEE-related events	
TEE-related esophageal bleeding/injury	TEE-related esophageal bleeding noted during or after TEE removal
Esophageal chemical burn	TEE-related injury to esophageal mucosa due to TEE cleaning chemicals
TEE-related airway compromise	TEE-related compromise of ventilation or oxygenation requiring removal of TEE
TEE-related extubation	TEE-related inadvertent extubation of the patient
Positioning-related	
Complications during patient transfer	Any event occurring during movement of the patient into/out of the procedure, such as loss of IV or arterial line, airway compromise, disconnection of lines
Peripheral nerve injury due to positioning	Temporary or permanent nerve injury noted postoperatively due to positioning during the procedure
Integument injury under anesthesia	Skin breakdown or dehiscence or alopecia noted postoperatively due to positioning during the procedure
Ocular injury (corneal abrasion or injury)	Ocular injury noted postoperatively, such as corneal abrasion
Regional anesthetic events	
Bleeding – regional anesthetic site	Bleeding at the site of regional anesthetic placement
Intrathecal puncture – regional	Inadvertent intrathecal puncture during caudal or epidural placement
Local anesthetic toxicity – regional	Systemic evidence of local anesthesia toxicity (ECG changes, CNS changes)
Neurologic injury – regional	Injury to the peripheral nerve during regional nerve block
Miscellaneous	
Anesthesia equipment malfunction/failure	Any anesthesia equipment malfunction or failure during the procedure
Unplanned need to remain intubated due to anesthesia	Need to remain intubated at the conclusion of the procedure due to anesthesia factors (oversedation, muscle relaxation)
Hypercyanotic episode ("Tet" spell)	Hypercyanotic episode (decrease in SpO_2 > 20% from baseline) requiring intervention other than establishing airway ("Tet" spell)
Pulmonary hypertensive crisis	Probable or definite PH crisis requiring intervention
Postoperative nausea/vomiting	PONV requiring unplanned admission
Vomiting / Aspiration	Vomiting or aspiration of gastric contents at either induction or emergence of anesthesia
Intraoperative recall	Recall of intraoperative events
Emergence delirium requiring medication	Emergence agitation or delirium requiring medication
Other	Any event related to anesthesia care not otherwise listed

Aline, arterial line; CNS, central nervous system; CPR, cardiopulmonary resuscitation; CVL, central venous line; ECG, electrocardiogram; ETT, endotracheal tube; ICU, intensive care unit; LMA, laryngeal mask airway; PH, pulmonary hypertension; PIV, peripheral intravenous catheter; PONV, post-operative nausea/vomiting; SpO_2, pulse oximeter oxygen saturation; TEE, transesophageal echocardiography; TOF, tetralogy of Fallot.
Source: Data fields are from Vener et al. [26].

International efforts

Efforts are ongoing to make this database initiative a global project. Initial collaborative discussions have taken place about the possibility of linking this initiative with the European Association of Cardiothoracic Anaesthesiology and Intensive Care [72]. The final selection of database fields will be made through a collaborative effort involving surgeons and cardiologists from Europe and North America, as well as other continents. It is certainly possible and desirable that the STS-CHSD has an identical anesthesia module in the congenital heart database of EACTS and The European Congenital Heart Surgeons Association. These European and North American congenital heart surgery databases have functioned as sister databases with identical nomenclature and database fields and definitions [73, 74]. The incorporation of anesthetic data into the effort should follow a similar strategy. This project should also ideally spread beyond North America and Europe. Efforts to involve Africa, Asia, Australia, and South America are necessary and already underway, under the leadership of The World Society for Pediatric and Congenital Heart Surgery [75].

The creation of a joint cardiac surgery and anesthesia database is another step toward the ultimate goal of creating a database for CHD that spans both geographic and subspecialty boundaries and can potentially capture a patient's lifetime of cardiac care regardless of their location. The Pediatric Heart Network, a research consortium of major congenital cardiac centers, has recognized this need and is supporting the creation of linkage between various registries such as the CCAS, STS, EACTS, Congenital Heart Surgeons' Society, the ACC IMPACT Interventional Cardiology registry, and the Pediatric Cardiac Critical Care Consortium (PC^4) ICU registry, as well as others [76].

Measuring outcomes has become a critical component of all facets of medical practice today. It is important for anesthesia and, in particular, for practitioners of pediatric cardiac anesthesia because of the extremely high-risk nature of this practice. Regular review of both caseload and outcomes in a structured manner through quality improvement conferences, mortality and morbidity, and individual case reviews can help to educate anesthesia departments and individuals and perhaps minimize future adverse outcomes. Open lines of communication with our surgeons, cardiologists, and intensive care physicians are a key component of this process, along with the recognition that adverse events are inevitable in such a system and our job is to always be vigilant and ready to act on the patient's behalf.

KEY POINTS: NETWORKS AND DATABASES

- A major database effort has been initiated by CCAS in conjunction with the STS Congenital Heart Surgery Database.
- Both cardiac surgical and non-cardiac surgical anesthetics can be entered, and 66,655 anesthetics from over 60 US programs have been analyzed as of 2020.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 de Leval MR, Carthey J, Wright DJ, et al. Human factors and cardiac surgery: a multicenter study. J Thorac Cardiovasc Surg 2000;119:661–72.
The landmark study of human factors in cardiac surgery detailing the incidence of near-misses and adverse events for the arterial switch operation.

20 Vener DF, Gaies M, Jacobs JP, Pasquali SK. Clinical databases and registries in congenital and pediatric cardiac surgery, cardiology, critical care, and anesthesiology worldwide. World J Pediatr Congenit Heart Surg 2017;8:77–87.
An excellent overview of existing and planned databases and registries in congenital heart disease, and the actual and potential combined database capabilities.

33 Vener DF, Guzzetta N, Jacobs JP, Williams GD. Development and implementation of a new data registry in congenital cardiac anesthesia. Ann Thorac Surg 2012;94:2159–65.
Description of the design, data fields, and processes for data collection, validation, and analysis in the first database of congenital cardiac anesthesia cases.

34 O'Brien SM, Clarke DR, Jacobs JP, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. J Thorac Cardiovasc Surg 2009;138:1139–53.
The description of the STAT mortality score modelled utilizing over 70,000 records from two databases, and dividing pediatric cardiac surgical procedures into five levels of mortality categories based upon the observed outcomes rather than a priori assignment by expert opinion. This process was then validated by comparison to a larger sample set of over 111,000 pediatric cardiac surgical cases.

35 Odegard KC, DiNardo JA, Kussman BD, et al. The frequency of anesthesia-related cardiac arrests in patients with congenital heart disease undergoing cardiac surgery. Anesth Analg 2007;105:335–43.
A detailed description of anesthetic-related cardiac arrests from a single-center prospective registry of cardiac anesthetics.

36 Flick RP, Sprung J, Harrison TE, et al. Perioperative cardiac arrests in children between 1988 and 2005 at a tertiary referral center: a study of 92,881 patients. Anesthesiology 2007;106:226–37.
An important description of a large single-center database of pediatric anesthetics demonstrating a 30-fold increase in mortality for pediatric cardiac surgery vs. non-cardiac surgery.

38 Jenkins KJ, Gauvreau K. Center-specific differences in mortality: preliminary analyses using the Risk Adjustment in Congenital Heart Surgery (RACHS-1) method. J Thorac Cardiovasc Surg 2002;124:97–104.
The description of the RACHS score, the first risk adjustment system for congenital cardiac surgery.

40 Lacour-Gayet F, Clarke D, Jacobs J, et al. The Aristotle score: a complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg 2004;25:911–24.
The description of the Aristotle score, the second published system for risk assessment in congenital heart surgery.

43 Jacobs ML, Jacobs JP, Thibault D, et al. Updating an empirically based tool for analyzing congenital heart surgery mortality. World J Pediatr Congenit Heart Surg 2021;12:246–281.
The latest iteration of the STAT score for surgical complexity and mortality in congenital heart surgery.

49 Bergersen L, Gauvreau K, Foerster SR, et al. Catheterization for congenital heart disease adjustment for risk method (CHARM). JACC Cardiovasc Interv 2011;4:1037–46.
An important work describing a risk assessment method for interventional cardiac catheterization, using data generated from five large cardiac catheterization centers in the US.

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51 Martin GR, Anderson JB, Vincent RN. IMPACT registry and national pediatric cardiology quality improvement collaboration: contributions to quality in congenital heart disease. World J Pediatr Congenit Heart Surg 2019;10:72–80.
A description of the IMPACT registry for cardiac catheterization outcomes and risk factors.

58 Odegard KC, Bergersen L, Thiagarajan R, et al. The frequency of cardiac arrests in patients with congenital heart disease undergoing cardiac catheterization. Anesth Analg 2014;118:175–82.
An important single-center prospective registry of cardiac catheterization anesthetics, with a detailed description of cardiac arrests and associated factors.

62 Ramamoorthy C, Haberkern CM, Bhananker SM, et al. Anesthesia-related cardiac arrest in children with heart disease: data from the Pediatric Perioperative Cardiac Arrest (POCA) registry. Anesth Analg 2010; 110:1376–82.
An important analysis of the POCA registry demonstrating that 34% of arrests were in patients with heart disease, and delineating the highest risk cardiac lesions.

CHAPTER 4

Multidisciplinary Collaboration, Team Functioning, and Communication in Congenital Cardiac Care

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Introduction

Caring for the patient with congenital heart disease (CHD) has become an increasingly complex endeavor, with the rapid increase in knowledge about each condition, and the diagnostic and therapeutic options available. Previously unimaginable procedures, such as a Stage I Palliation procedure for hypoplastic left heart syndrome (HLHS) being performed interventionally in the cardiac catheterization laboratory without surgery, are being contemplated and will be attempted soon [1]. Congenital cardiac care now encompasses the entire lifespan from the fetus and neonate to the adult with CHD [2]. The explosion of knowledge in pediatric and CHD makes it impossible for one practitioner, or a small group of caregivers, to possess the requisite knowledge about every condition to make an informed decision for the best care of the patient. Newer procedures such as transcatheter pulmonary and aortic valve replacement, stenting or occlusion of the patent ductus arteriosus (PDA) in small infants, and a variety of new short- and long-term mechanical support devices have radically changed the older approaches to many lesions and clinical scenarios which formerly had been well established [3, 4]. There is a profusion of outcome studies of all of these new approaches published every year, and it is infeasible to be well versed in all of these new data. Over the past several decades, the development of pediatric and congenital cardiac anesthesiology, with a more formal and complete knowledge base, dedicated teams in many centers, and organized fellowship training now culminating in Accreditation Council for Graduate Medical Education (ACGME) certification in the United States, has given impetus for anesthesiologists to be formally involved in patient care decision-making and leadership roles in systems of care [5]. The idea of multidisciplinary collaboration, where many experts discuss and contribute to patient care decisions and reach a consensus, has evolved as the desired model for many institutions, given the profound implications for outcomes and quality of life for patients. In addition, collaborative shared leadership for strategic and operational planning has emerged as a desired model in congenital cardiac care for many programs.

This chapter will review the concept of a Center for care in congenital cardiac disease from the perspective of the Texas Children's Hospital (TCH) Heart Center as an example of one possible approach to multidisciplinary collaboration of a large number of providers from many disciplines, and its evolution over 25+ years. Undoubtedly, there are many varied paths

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taken by different institutions to achieve their current CHD programs, and TCH is but one example [6, 7]. The congenital cardiac anesthesiologists' essential role as not only caregivers, but also as contributors to patient care decision making, and TCH Heart Center leadership, will be highlighted. Then, important issues in communication and team functioning in the periprocedural areas will be discussed, focusing on the anesthesiologist's role in the cardiac surgical operating rooms (OR) and catheterization laboratories, and in the handoff of information postprocedure, to the intensive care unit (ICU) caregivers. Next, additional examples of multidisciplinary programs and teams will be described. Finally, a brief discussion of the COVID-19 pandemic on team functioning in congenital cardiac care is presented.

Texas Children's Heart Center multidisciplinary approach

Over the past 25+ years, Texas Children's Hospital congenital cardiac care has evolved from a small team of one surgeon, one anesthesiologist, three perfusionists, two OR nurses, and 10–15 cardiologists (many of whom doubled as cardiac intensivists), performing 450 surgeries and 500 cardiac catheterizations per year, to the current large system of seven surgeons, 14 anesthesiologists, 60 cardiologists, and 25 cardiac intensivists performing more than 1,000 surgeries, and 1,500 cardiac catheterizations annually. What formerly was essentially 2–3 possible personnel combinations for cardiac surgery, with great familiarity of the same team working together at least several times a week, has evolved into an almost infinite number of caregiver combinations where the same team is only infrequently together. The TCH Heart Center has developed a robust system of leadership, care, and communication that has enabled this evolution, from a simple system to a large complicated organization, and now to a very large complex organization, where all personnel strive to provide a consistent, high-quality level of care to all patients. The concept of complex adaptive systems in health care is being realized [8], where the focus is on interactions of interdisciplinary team members with each other, rather than on the characteristics of individual team members, in their ability to adapt to the many changing conditions and challenges to the organization [9].

Heart Center leadership structure

The TCH Heart Center Executive Committee (HCEC) consists of two Co-Directors, the Service Chiefs of Congenital Heart Surgery, and Pediatric Cardiology. Additional members include the Service Chiefs of Congenital Cardiac Anesthesiology (CCA) and Cardiac Intensive Care. Finally, a Nursing Lead, Physician Business Development lead, Hospital Administrative Director, and several Leads for Philanthropy and Public Relations complete the Committee (Table 4.1). This committee meets monthly or more often as needed, to set strategic directions and respond to current challenges. Of note, CCA has a major role "at the table" for all of these meetings and has an opportunity to contribute to all major questions facing the HCEC. The HCEC has a reporting relationship to a TCH Senior Leadership team consisting of the In-Chiefs of the six hospital medical staff departments, and Executive Vice Presidents. Reporting to the HCEC are six multidisciplinary teams, each with representation from all major disciplines, that encompass the major priorities of the TCH Heart Center: clinical operations, research operations, teaching operations, data operations, patient and family experience, and marketplace competition.

Table 4.1 Texas Children's Heart Center multidisciplinary leadership structure

Heart Center executive committee members:
- Chief of Pediatric Cardiology, Co-Director
- Chief of Congenital Heart Surgery, Co-Director
- Chief of Congenital Cardiac Anesthesiology
- Chief of Cardiac Intensive Care
- Business Development Lead (Physician)
- Nursing Lead
- Hospital Administrative Lead
- Philanthropy Lead
- Marketing/Public Relations Lead

Multidisciplinary distributive leadership teams:
- Clinical operations
- Teaching operations
- Research operations
- Patient and family experience
- Marketplace competition
- Data operations

Clinical decision-making

The TCH Heart Center has made a commitment that every patient presenting for a potential intervention, whether surgery or cardiac catheterization, should be presented before a wide audience of Heart Center members, and the clinical decision-making conferences are open to all members of the TCH Heart Center. The only exception is an emergency case where time does not permit broad discussion or simple diagnostic catheterization cases that are scheduled per protocol such as myocardial biopsies. There is formal Heart Center time every day, Monday through Friday, to present new cases in need of a timely decision about surgery, catheterization, or complex medical care.

Presurgical planning conference

Presurgical planning conferences have remained a key component of congenital cardiac care for well over 50 years and are a familiar feature of most pediatric cardiology/cardiac surgery programs [10]. Traditionally this approach involved only cardiology and surgery; for example, in the author's experience at the University of California, San Francisco, during Pediatric Residency training in the 1980s, a Cardiology Fellow would present the history and physical examination findings, and the additional data such as ECG, chest radiograph, cardiac catheterization angiograms and physiologic calculations, and laboratory data. In later years, echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) results were added to the data presented. After this presentation, a surgical plan was made after discussion among the (usually senior) cardiologists and surgeons. The junior

members of the team were reluctant to speak and rarely did so. Duignan and colleagues prospectively evaluated clinical decision-making in 107 consecutive patients in a joint Pediatric Cardiology-Cardiac Surgery Conference, deeming 50% of the cases as complex [11]. Among these patients, Duignan and colleagues identified occasional patients with the same data sets that had different clinical decisions, some instances of the same complex patient being revisited, and two different treatment plans resulting. Anchoring bias (tendency to recommend procedures within one's own field, i.e. surgery or interventional catheterization) was identified in several cases, and the lack of validated decision-making algorithms in the field of congenital cardiac care was noted. The TCH Heart Center has attempted to minimize these issues with the following approaches.

At TCH, Surgical Case Conferences reviewing upcoming cases for the week have involved anesthesiologists, intensivists, nurses, consultants, radiologists, trainees in all disciplines, and any other interested clinician in the Heart Center for over 25 years; and in pre-COVID 19 pandemic times often over 100 people gathered in the Helen B. Taussig Auditorium to discuss and confirm, and at times alter, the surgical plan (Figure 4.1). A structured template, with a clinical presentation by the cardiology, surgery, or intensive care fellow, followed by the display of pertinent imaging findings by an echocardiographer, or cardiac MRI/CT specialist dedicated for the conference and prepared in advance, is followed by proposed surgical plan and discussion, confirming or at times changing the plan. Ninety minutes on Monday morning is allotted to the presentation of approximately 15–20 patients; requiring presentation and discussion to be efficient and accomplished in 3–5 minutes for the straightforward patients. In the COVID-19 pandemic era, this and all large Heart Center Conferences have been converted to a videoconference format (Figure 4.2). In both settings, all attendees are encouraged to voice their opinions about the proposed plan for a case, even if they are a member of the junior faculty or trainee groups.



Figure 4.1 Texas Children's Hospital surgical case conference. (A) Pediatric cardiology fellow presenting the history and physical exam findings of a neonatal patient scheduled for cardiac surgery. (B) View of the surgical case conference audience, with chest radiograph displayed. (C) Large-scale high-resolution digital screens allow accurate review of angiograms from the Cardiac Catheterization Laboratory. (D) Cardiac magnetic resonance imaging is presented.

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Figure 4.2 Desktop computer view during urgent case presentation of the neonate with hypoplastic left heart syndrome requiring surgery. The echocardiogram is being discussed via videoconference during the COVID-19 pandemic era.

New patient case conferences

Additional clinical decision-making opportunities exist for new patients, and existing patients requiring decisions about the next steps in clinical care. Further, 90 minutes each on Monday and Wednesday afternoons are allotted to two such conferences, where primary cardiologists present to representatives from Cardiac Surgery and Catheterization Laboratory, to decide on a treatment plan.

A specialized conference for Adult Congenital Heart Disease (ACHD) patients is held once a week for 60 minutes, where a multidisciplinary group discusses the unique needs of this patient group, including medical, catheter, and surgical therapy. Representatives from surgery, ACHD cardiology, ACHD ICU, anesthesia, and nursing are present in these weekly conferences. As with the other patient decision-making conferences, the entire Heart Center is invited to attend these conferences.

Morning report

In addition to these formal conferences, each day starts with a morning report where the entire Heart Center can attend; after a brief review of the inpatient Heart Center census and planned admissions and discharges there is an opportunity to present newly admitted patients, or patients otherwise in need of clinical treatment decisions urgently (within 24–48 hours) who cannot wait for the formal case conferences (Figures 4.2 and 4.3). As with the formal planning conferences, any attendee is encouraged to speak up and voice their views on a proposed treatment plan, and at the end of the presentation, a consensus is reached about the planned treatment. These presentations often result in cases added to the surgical or catheterization schedule the same day as the presentation. For example, on the day of this chapter writing, an infant with tetralogy of Fallot, and PDA stent with cyanotic spells was presented in morning report, and dilation of PDA stent vs. surgery was discussed, the consensus was for surgery and successful repair was accomplished that day.

Data, validation, and consistency in clinical decision-making

This system of clinical decision-making has evolved as the TCH Heart Center has grown in numbers of cases handled and personnel available, so that every patient has the advantage of the collective experience and wisdom of the entire Heart Center through a transparent process striving to attain consistency in decision-making, e.g. all patients with the same condition will receive the same or similar treatment plan, that is data and outcomes-driven and widely known to all who have an interest. The above-noted Surgical Case Conference is an opportunity for a second review to confirm the surgical plan before the patient enters the OR and occasionally results in a change in the plan. Periodically, through additional Heart Center quality conferences noted below, outcome data for major lesions or other lesions of interest are reviewed, both for local cases, for large databases such as the Society of Thoracic Surgeons' Congenital Heart Surgery Database, and recently published literature. Through this process, a consensus is reached to change approaches to specific lesions. Two recent examples include the decision to move to primary stenting of the PDA for most neonates with right-sided obstructive lesions in need of a stable source of pulmonary blood flow instead of a Blalock-Taussig-Thomas shunt; and transcatheter occlusion of the PDA in premature and other small neonates instead of ligation by thoracotomy.

Monday September 13, 2021
7:00 AM

Date:	9/13/2021	Time:	7:00 AM	
Heart Center Inpatient Census Review				
Unit	Capacity	Starting Census	Ending Census	off-service
CICU	54	46	36	2
CPCU	48	42	39	6
ACHD	10	4	4	0
Totals:	*112*	*92*	*79*	*8*

Heart Center Activity Past 24 Hours		
CVOR		
Scheduled Cases	Cancelled	Cases Completed
4	0	5
Cath Lab		
Scheduled Cases	Cancelled	Cases Completed
5	0	5

Non-Scheduled Admissions Past 24 Hours		
Patient Name	Procedure / Diagnosis	From
	CICU	
	4 wk. w/PVS s/p pulm valvuloplasty and PDA stent and adrenal insufficiency/safety fast prior to d/c	CPCU RRT
	3 y.o. concern for MIS-C	EC
	3 wk.o. post-natal dx of CoA	EC
	13 m.o. TOF/hypercyanotic spells	CPCU RRT
	CPCU	
	6 y.o. cc-TGA s/p Fontan /fever. desaturations	EC
	13 y.o. w/ HIE and ICD malfunction/concern for GI bleed	West Campus
	3 m.o. AVSD, PVS, ASD, VSD, and bicuspid AS/FTT	main admit
	30 y.o. unpalliated DORV, VSD, depressed fxn and Eisenmenger Sydrome/SOB and tachycardia	EC
	ACHD	

(A)

Thursday September 9, 2021
7:00 AM

Heart Center Operations - Inpatient			Anticipated In						Anticipated Out		
Unit	Operational Capacity	Census	L&D	Cath	CVOR	Transport	Main Admits	Transfers In	Discharge	Transfers Out	Est. Ending Census
CICU (16, 17, 18)	54	44	0	0	3	0	0	0	0	5	42
CPCU (22, 23)	48	42	0	4	0	0	0	5	5	1	45
ACHD (24)	10	6	0	0	0	0	0	0	1	0	5
Totals:	**112**	**92**	**0**	**4**	**3**	**0**	**0**	**5**	**6**	**6**	**92**

Heart Center Operations - Outpatient		
Area	Visits/ Procedures	Disposition
Cardiology Clinic	76 clinic; 8 fetal	Home
ACHD Clinic	8 clinic; 8 ECHO	Home
CHS clinic	7 clinic	Home
Cath Lab	5	4 CPCU

Patient Name	Procedure / Diagnosis	To-From
	Rastelli procedure and BTS tkdn via median sternotomy	SDA-CICU
	median sternotomy, Repair of supravalvar AS, poss ascending aortic or aortic arch augmentation, PA augmentation	CPCU-CICU
	Valve sparing aortic root replacement	SDA-CICU
	trans catheter pulm valve placement	OP-CPCU
	trans catheter pulm valve placement	OP-CPCU
	trans catheter pulm valve placement	OP-CPCU
	trans catheter pulm valve placement, coronary angio	OP-CPCU

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(B)

Figure 4.3 Morning report. (A) An overview of heart center census and non-scheduled admissions. ACHD, adult congenital heart disease unit; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CICU, cardiac intensive care unit; CoA, coarctation of aorta; CPCU, cardiology-cardiac surgery inpatient ward; CVOR, cardiovascular operating rooms; DORV, double-outlet right ventricle; EC, emergency center; FTT, failure to thrive; GI, gastrointestinal; HIE, hypoxic-ischemic encephalopathy; ICD, implantable cardioverter-defibrillator; MIS-C, multisystem inflammatory syndrome in children associated with COVID-19; PVS, pulmonary valve stenosis; PDA, patent ductus arteriosus; RRT, rapid response team; SOB, shortness of breath; TGA, transposition of the great arteries; VSD, ventricular septal defect (B) Anticipated admissions and discharges to inpatient units, and scheduled clinic visits. CHS, congenital heart surgery; ECHO, echocardiography laboratory; OP, outpatient; SDA, same-day admission.

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Although the field of validated decision-making algorithms in CHD is relatively new, one example is an approach developed at TCH for Anomalous Aortic Origin of the Coronary Arteries (AAOCA), where the three treatment strategies are: observation without exercise restriction; exercise restriction; and surgical intervention [12]. Using decision analysis, a formal quantitative approach that analyzes different management strategies under conditions of uncertainly, an algorithm was developed utilizing outcomes from the published literature, and individual patient characteristics such as age and symptomatology. Life expectancy and quality-adjusted life expectancy were the outcomes, and a cohort of 10,000 hypothetical identical patients underwent a first-order Monte Carlo simulation, with further sensitivity analyses. Surgery was the preferred management strategy for most patients under 30 years of age for anomalous left coronary artery; and for patients <25 years of age for anomalous right coronary. Utilizing the principles proposed in this algorithm, 47 of 163 patients with AAOCA underwent surgery; 82% of the entire group was allowed unrestricted sports exercise activity; and of the surgical patients, 3 (6.4%) are restricted from sports exercise activity(Figure 4.4) [13]. All patients in the cohort were alive, whether they underwent surgery or not, during the follow-up period. The formation of a multidisciplinary team, with support from clinical data science specialists, is key to the success of this program.

Multidisciplinary Surgical Patient ICU Rounds

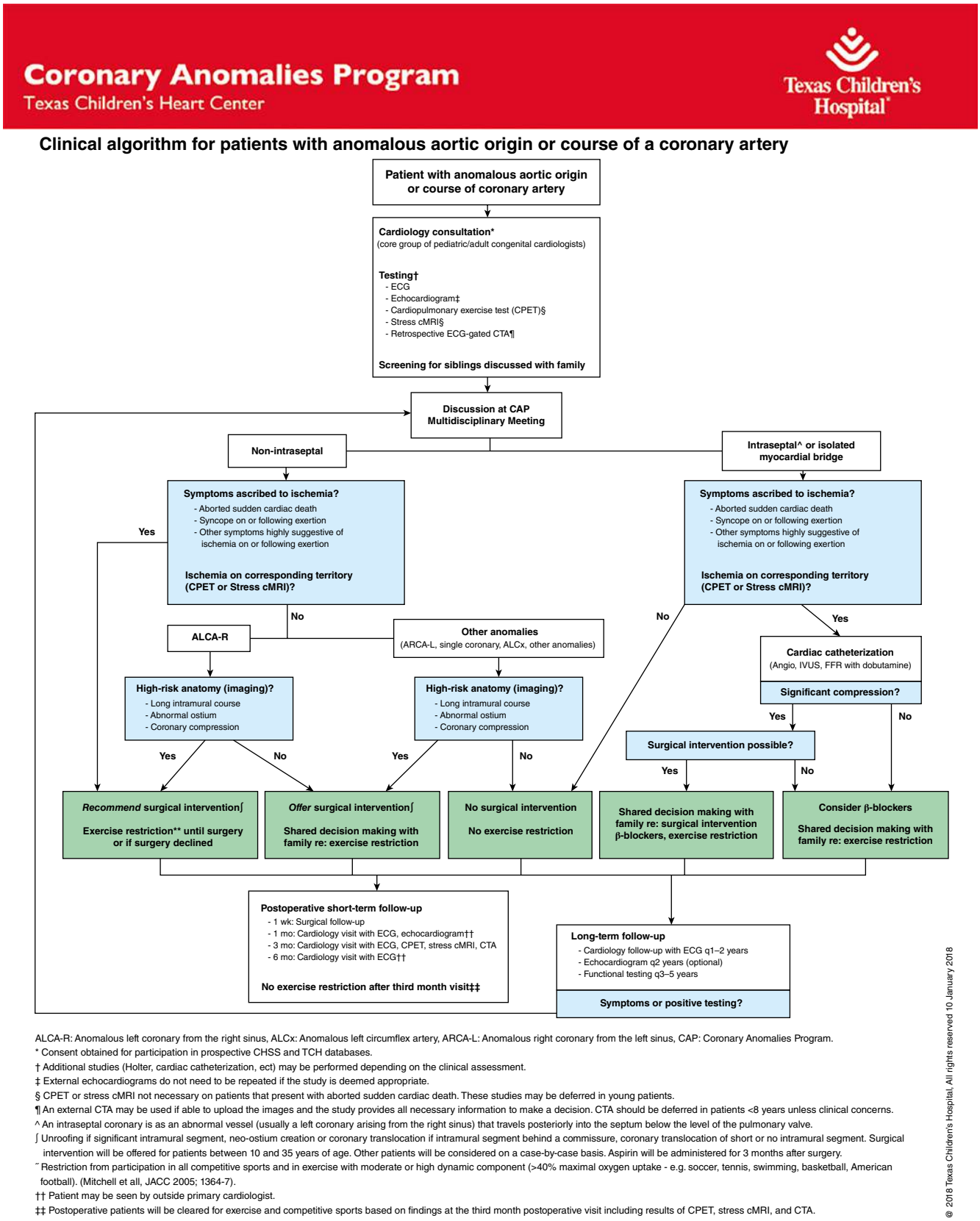
Because of the early start to the surgical cases and the additional early morning conferences, the practice of rounding on surgical patients in the Cardiac ICU (CICU) at 6:15 AM Monday–Friday has been practiced for many years. This has resulted in a large group of surgeons, surgical trainees, advanced practice providers, CICU physicians and trainees, nursing leadership, the bedside nurse, and even the parents present in (or mostly outside in the hall) the CICU, traveling from patient to patient. A brief, standardized presentation by the ICU, surgical, and nursing providers for the patient was followed by surgical plans, i.e. removal of the chest tubes, pacing wires, sternal closure, etc. for the day. It was typical to have limited sight and hearing lines to the presenter, the patient, the displayed radiographs, and the physiological monitors. The COVID-19 pandemic has prevented the gathering of large groups near the bedside and given rise to some novel methods to present the patient's data to a multidisciplinary group. At the time of this writing, Surgical Rounds are conducted over videoconferencing with all participants (20–40 on most days) logged in at their respective desks. The presenters communicate the data, while the chest radiograph and real-time physiologic monitoring data are displayed on the screen (Figure 4.5). Joint decisions are made about surgical and major ICU issues, with all participants able to see and hear all the data, and with the ability to speak up to allow their perspectives to be communicated. The process is also more efficient in this manner, with as many as 30–40 active surgical patients presented in the allotted 45 minutes. The entire Heart Center is invited to these rounds, as with all of the other major patient care conferences.

Heart Center Quality Improvement Conferences

The TCH Heart Center has several patient care Quality and Outcomes Improvement Conferences, which are protected in a legal framework from disclosure and outside discovery, allowing detailed and frank discussion of quality issues. Most of these conferences include the entire Heart Center on the invitation list.

Performance Rounds

Once per week a 60-minute meeting is devoted to Performance Rounds, where selected patients from surgery or the catheterization laboratory are presented in a standardized, visual, infographic time-based format where the horizontal axis is time (days) and the vertical axis is the perceived risk level to the patient, from threats, errors, unintended clinical states and their linkage; risk increases with the intensity of the activity and decreases with the de-escalation of care (Figure 4.6). Increased risk is conferred during surgery, generally the highest risk state in a patient's journey, and decreased with tracheal extubation, sternal closure, weaning off inotropes, discharge to ward, and discharge to home. Data is collected from electronic medical records, bedside data, adverse event reporting mechanisms, and staff interviews. This approach was described by Hickey and colleagues, who reported on 524 patient care "flights" surrounding a surgical procedure [14]. In 12% of flights the patients failed to de-escalate sequentially, and in the timeframe expected, through the risk levels. Failed de-escalations were strongly associated with errors (426 in 257 flights, $p < 0.0001$). More serious errors were associated with the 29% rate of failed de-escalation, vs. 4% in flights with no consequential error ($p < 0.0001$). Using this process at the TCH Heart Center, outcomes data for the major procedures have been developed, both internal center-specific outcomes, and from national databases such as the Society of Thoracic Surgeons' Congenital Heart Surgery Database. A team of outcome specialists develops the infographics and presents the data, and the entire Heart Center staff is invited. In recent years interventional cardiac catheterization procedures have been added to Performance Rounds. Before these rounds, the themes of psychological safety (see below), and confidentiality of the privileged patient care information are emphasized. Surgeons', cardiologists', and anesthesiologists' names are listed on the infographic, and they are encouraged to explain any unexpected events for the benefit of the entire Heart Center, with the goal of collective learning, communication, and improving patient care, and not to direct blame to the individual practitioner. Themes and issues that are identified, i.e. communication errors, delayed care, technical errors, decision-making errors, etc., are discussed, and if emerging patterns are perceived over multiple patients, they are referred formally to the Quality and Outcomes Team for a deeper dive into causes and solutions. These issues are brought back to the Heart Center for updates on changes to processes and outcomes. Routine simple surgery or catheterization laboratory cases, without unexpected progress in de-escalation, are presented in a list format but not otherwise discussed.



ALCA-R: Anomalous left coronary from the right sinus, ALCx: Anomalous left circumflex artery, ARCA-L: Anomalous right coronary from the left sinus, CAP: Coronary Anomalies Program.
* Consent obtained for participation in prospective CHSS and TCH databases.
† Additional studies (Holter, cardiac catheterization, ect) may be performed depending on the clinical assessment.
‡ External echocardiograms do not need to be repeated if the study is deemed appropriate.
§ CPET or stress cMRI not necessary on patients that present with aborted sudden cardiac death. These studies may be deferred in young patients.
¶ An external CTA may be used if able to upload the images and the study provides all necessary information to make a decision. CTA should be deferred in patients <8 years unless clinical concerns.
^ An intraseptal coronary is as an abnormal vessel (usually a left coronary arising from the right sinus) that travels posteriorly into the septum below the level of the pulmonary valve.
∫ Unroofing if significant intramural segment, neo-ostium creation or coronary translocation if intramural segment behind a commissure, coronary translocation of short or no intramural segment. Surgical intervention will be offered for patients between 10 and 35 years of age. Other patients will be considered on a case-by-case basis. Aspirin will be administered for 3 months after surgery.
¨ Restriction from participation in all competitive sports and in exercise with moderate or high dynamic component (>40% maximal oxygen uptake - e.g. soccer, tennis, swimming, basketball, American football). (Mitchell et all, JACC 2005; 1364-7).
†† Patient may be seen by outside primary cardiologist.
‡‡ Postoperative patients will be cleared for exercise and competitive sports based on findings at the third month postoperative visit including results of CPET, stress cMRI, and CTA.

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Figure 4.4 Texas Children's Hospital Heart Center Coronary Anomalies Program Algorithm for patients with the anomalous aortic origin of a coronary artery.

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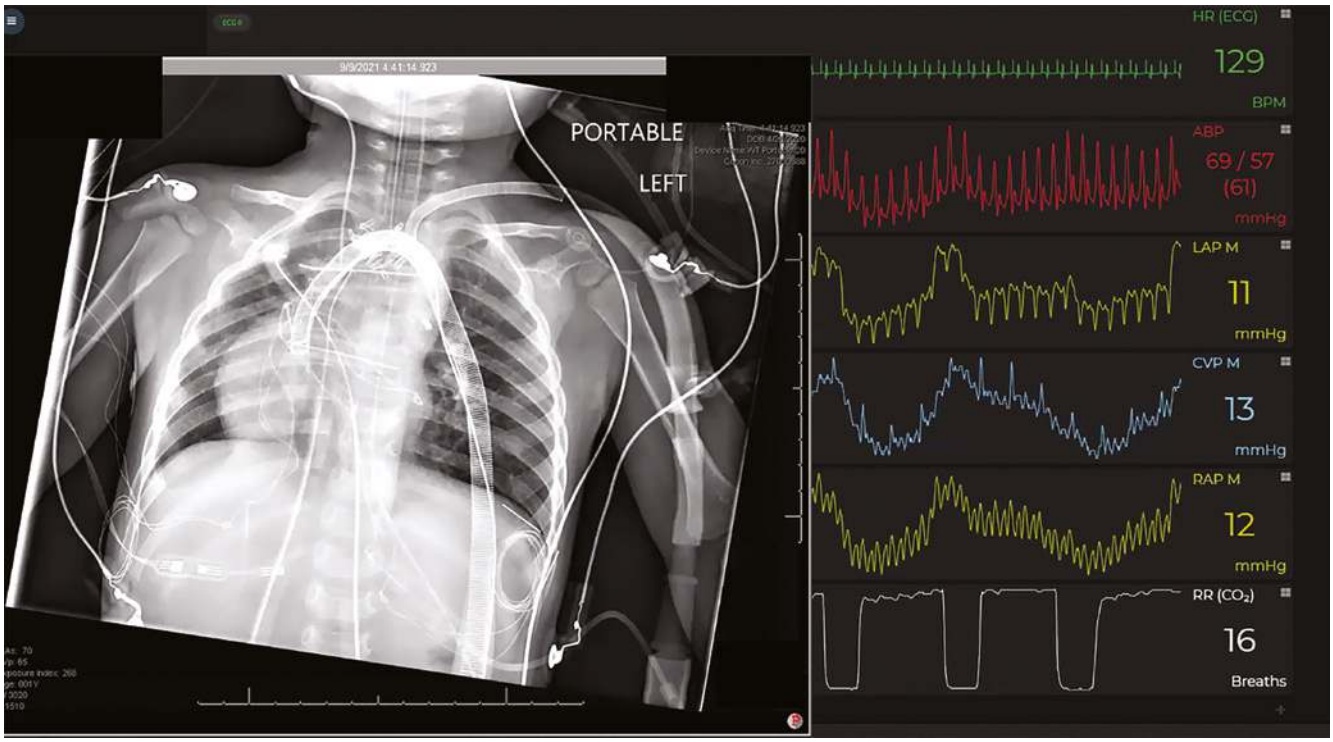


Figure 4.5 Videoconference screen during surgical rounds on a patient on ECMO support. The surgical fellow is presenting data while chest radiograph and real-time monitoring data are displayed during the COVID-19 pandemic era.

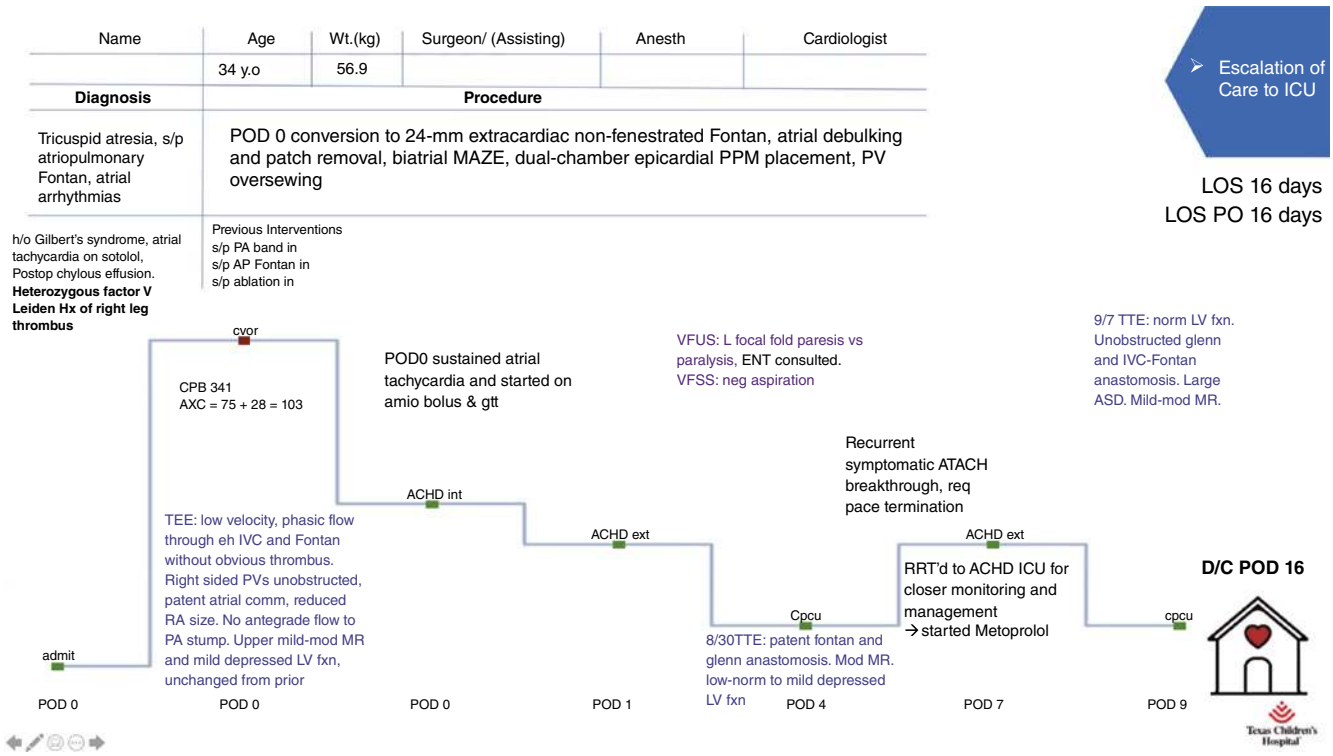


Figure 4.6 Performance rounds infographic. Time in days is displayed on the horizontal axis; risk level on the vertical axis; and details of the operative course are reported. The upper right-hand corner displays the major event prompting discussion; in this case, an arrhythmia requiring readmission to ICU which was recognized and treated appropriately. Note the stepwise decrease in risk level until postoperative day 7.

Heart Center Quality Conference

Once per week a 60-minute conference is devoted to quality and outcomes data and reports from each of the clinical disciplines in the Heart Center, on a rotating basis. This includes a Surgical Morbidity and Mortality conference, Catheterization Laboratory Quality Conference, CICU Quality and Outcomes presentation, Cardiovascular Anesthesiology Quality Presentation, and presentations from Nursing, Adult CHD, Outpatient Cardiology, Echocargiography, and other components of the Heart Center clinical enterprise.

Multidisciplinary meeting

Every Friday early morning, 45 minutes are devoted to a Quality and Outcomes Multidisciplinary Meeting, where only the attending physicians from Surgery, Anesthesiology, and CICU, plus a Nursing and Perfusion leader, are invited, for a discussion of each surgical case done in the past week, to review the immediate perioperative course and outcomes, communicate common important issues to the group, and give each member an opportunity to discuss their decision-making process and how it may have contributed to the outcome. The surgeon starts by briefly presenting the case, and then the anesthesiologist and intensivist have an opportunity to add to the discussion. The smaller group is conducive to frank discussions about opportunities for improvement; identifying significant issues that affect the entire perioperative team that then can be assigned an individual to lead more data collection and solutions to the problem. Great successes are also discussed and celebrated, and those involved in the case can enlighten the group, again for the benefit of future patients.

Figure 4.7 displays the calendar of the weekly multidisciplinary meetings in the TCH Heart Center.

Heart Center Wide Communication Activities

Heart Center Town Hall

With a very large group of practitioners and supporting staff that now numbers greater than 500 individuals, it can be challenging to communicate important events, announcements, initiatives, and strategies to all Heart Center members. Quarterly Heart Center Town Halls, 60 minutes in length, are held, with the Heart Center Executive Committee leadership leading the agenda and introducing additional speakers; there are always at least 15–20 minutes left for comments and questions, and unanswered questions are addressed separately by email (Figure 4.8).

Heart Center annual retreat

Once every year, non-emergent patient care is paused for 4 hours, and the entire Heart Center participates in a "retreat" – in reality on site at TCH. During these retreats, a theme is prepared, and after Heart Center leadership presentations, speakers from the Heart Center, or outside speakers make presentations followed by questions and comments from the audience. Once again, all Heart Center members at any level of seniority are encouraged to ask questions and make comments, for the benefit of the entire group. Some annual retreat themes have included: improving communication across silos, integrating teams and processes, transparency, psychological safety, shared decision-making, patient/family experience, partnerships with external providers, and shared common purposes [15, 16]. In the pre-pandemic era, several hundred people gathered in a large auditorium and enjoyed well-prepared content, for example, presentations on psychological safety from a well-regarded Rice University School of Business professor with substan-

Time	Monday	Tuesday	Wednesday	Thursday	Friday
6:15–7 AM	Surgical Rounds	Surgical Rounds	Surgical Rounds	Surgical Rounds	Surgical Rounds/ Multidisciplinary Meeting*
7–7:10 AM	Morning Report, Urgent Cases	Morning Report, Urgent Cases	Morning Report, Urgent Cases	Morning Report, Urgent Cases	Specialty Specific Meetings
7:10–8 AM	Surgical Case Conference	Performance Rounds	Quality Conferences		
8–9 AM					Morning Report, Urgent Cases
3–4:30 PM	Monday Afternoon New Case Conference		Wednesday Afternoon New Case Conference		
5–6:00 PM		Adult CHD Case Conference			

All Heart Center members are invited to attend all conferences with the exception of the Multidisciplinary Meeting on Friday mornings. *Attending Surgeons, Anesthesiologists, Intensivists only. CHD, congenital heart disease.

Figure 4.7 Texas Children's Hospital Heart Center Multidisciplinary Conference Schedule.

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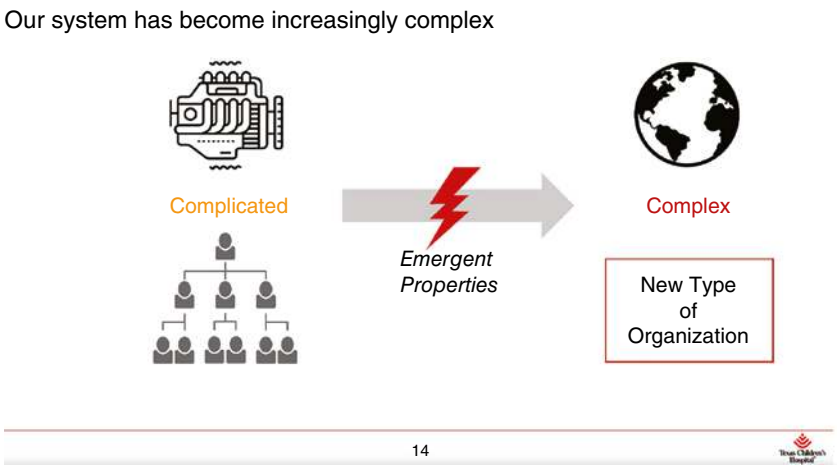


Figure 4.8 Slide from recent TCH Heart Center Town Hall in the COVID-19 pandemic era.

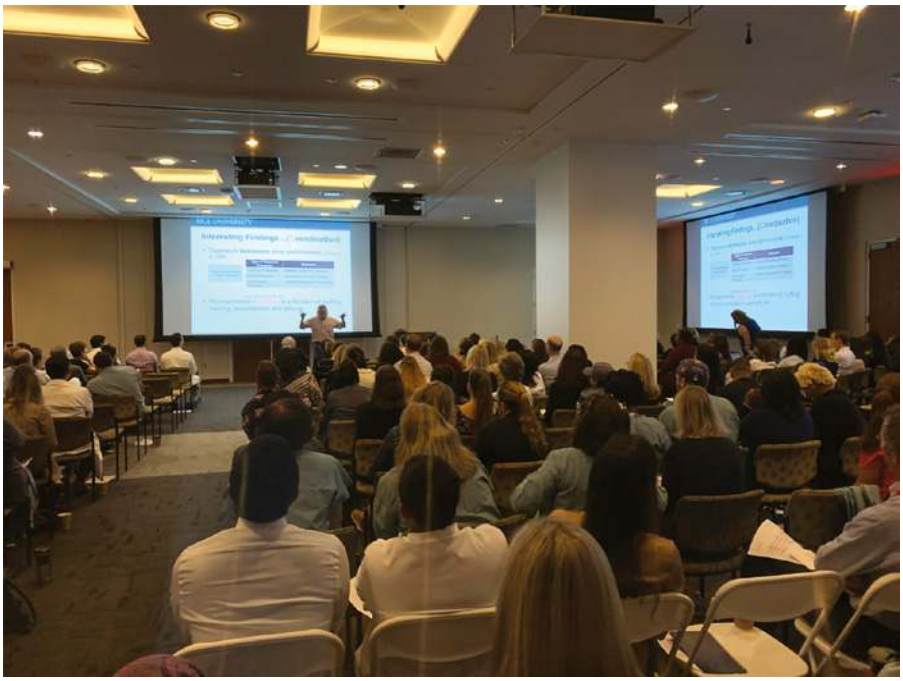


Figure 4.9 TCH Heart Center Retreat in the pre-pandemic era with an outside speaker presenting his research on team functioning in healthcare.

tive research in this area (Figure 4.9). In the current pandemic era, this activity is conducted by videoconference; with participants encouraged to write questions, or ask live if they prefer.

Anesthesiologist involvement in patient care and leadership activities

TCH Heart Center anesthesiologists are often busy starting cases for the early 7–8 AM conferences and cannot attend all, but all conferences have anesthesiology representation for those without scheduled cases at that time. The anesthesiologists very often contribute to the discussion and the decision-making process for all of these conferences and are valued full-time members of the Heart Center team, whose opinion is often requested and is always respected. Presence and visibility at these conferences for the Anesthesiologists give them complete access and exposure to the broader Heart Center, increasing respect and affording opportunities, rather than being limited to surgeons in the operating room and interventional cardiologists in the catheterization laboratory. Having a full-time division whose sole clinical activity is in the Heart Center also increases the reputation and trust of CCA, and affords leadership, quality, education and research opportunities that facilitate career advancement and satisfaction.

Communication and team functioning in periprocedural areas: surgery and catheterization laboratory

In 2000, de Laval and colleagues published a landmark paper on human factors, errors, near misses, communication, and rescue from negative events in a multicenter study of 193 arterial switch operations (ASO) performed by 21 surgeons in all 16 institutions performing pediatric cardiac surgery in the United Kingdom in the late 1990s [17]. A self-assessment questionnaire regarding performance was filled out at the end of the operation by the surgeon and surgical assistant, the anesthesiologist, perfusionist, and scrub nurse. Each case was independently observed by a human factor researcher, who wrote a detailed description of the operation, including individual and team performance, communication within and between teams, and situational and organizational data. Errors or failures were recorded and classified as minor (minor disruptions in surgical flow without consequences) or major (likely to have serious patient safety consequences) negative events. Events were also deemed compensated, or uncompensated, meaning resolved, or recovered after appropriate action by the perioperative team. There were 16 hospital deaths for mortality of 6.6% with 43 near misses (17.7%). The number of uncompensated major events per case conferred the strongest risk of death at an odds ratio of 13 (95% CI 2.1–83, $p = 0.006$), and for each uncompensated major event, estimated odds of death increased by a factor of 5.7, and odds of death plus near miss were increased by a factor of 40. Interestingly, the self-report questionnaires were not successful in capturing human factors in predicting outcomes. The finding that failure to rescue from complications was strongly associated with poor outcomes is consistent across medical specialties. The list of observed major and minor events in this paper details a number of team performance problems, e.g. not communicating significant deterioration during cannulation, delay in the administration of heparin, delay in recognition of myocardial ischemia post-CPB, incorrect interpretation of serious deterioration during transport to ICU, failure to achieve sufficient vascular access, the inappropriate delegation of anesthetic tasks to inexperienced juniors, and many others (Table 4.2). This widely cited study described in great detail the gaps in performance during a highly complex, but very reproducible operative procedure. The study serves as a roadmap to better team functioning and communication and has contributed to the ability not only to rescue from errors but even more important to prevent them from occurring in the first place.

Table 4.2 List of observed major and minor events during the arterial switch operation

Stage (No.)	Description and examples
Major events Preoperative (4)	Serious errors and problems that are experienced before anesthetic induction for surgery, e.g. cardiac perforation during balloon atrial septostomy(BAS)
Anesthesia (8)	Errors and problems experienced during anesthesia and insertion of lines • Failure to gain sufficient vascular access • Pincushioning during insertion of lines, leading to a serious cardiac event • Delayed diagnosis of a major deterioration in the patient's condition • Lack of monitoring delaying diagnosis of a serious event
Prebypass (27)	• Hemodynamic instability of the patient due to rough surgical manipulations • Surgical errors, e.g. laceration of the ductus arteriosus before bypass • Serious cannulation problems • Severe unrecognized deterioration in the patient's condition (low ABP and SaO_2) before bypass caused by cognitive tunnel vision on surgical tasks and/or lack of monitoring • Delay in the administration of heparin
Bypass (44)	• Decision-making errors in deciding how to reimplant a difficult CAP (inexperienced surgeons) • Technical errors: aortic tear during the administration of the cardioplegic solution, accidental injury to a major coronary artery, malrotation of the main pulmonary artery, twisting the pulmonary artery during the Lecompte maneuver, damage to the neo-aortic valve, tear during the closure of the ductus arteriosus, severe laceration of a pulmonary arterial branch requiring patch repair • Major perfusion problems • Anesthetic problems: failure to cool the cardioplegic solution, failure to flush the cardioplegia-infusion set resulting in massive coronary air embolism
Postbypass (84)	• Serious ischemic event: delay in diagnosis, incorrect interpretation, inappropriate strategy in the event of a serious ischemic event • Ventilation errors by consultant anesthetist • Surgical omissions; omission of pacing wires in a patient who has severe arrhythmias, omission of securing indwelling catheters such as the left atrial line • Delayed diagnosis; incorrect interpretation of a serious deterioration of the patient during the transfer from the operating theater to the ICU
Minor events Preoperative (17)	• Coordination problems with the blood bank, problems with the availability of ICU beds • Communication problems between the ward and the theater team, scheduling of cases • Poor fasting policy

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Table 4.2 (Continued)

Stage (No.)	Description and examples
Anesthesia (67)	• Cognitive tunnel vision on insertion of lines to the neglect of monitoring the ECG screen (where no major event results) • Inappropriate delegation of anesthetic tasks to an inexperienced junior • Equipment problems: failed alarm systems, incorrect ECG readings, or unavailability of equipment • Human resource problems, e.g. no junior anesthetic assistant available, no technical assistance
Prebypass (144) and bypass (732)	• Positioning and tension error(s) by the surgical assistants • Instrument handing errors by the scrub nurse • Distracters: internal and external • Inappropriate task delegation (surgical, anesthetic, perfusion) to an inexperienced assistant • Problems with theater equipment • Communication errors: problems with passing information between theater teams • Absence of a senior team member in theater at safety-critical times • Surgical tunnel vision, where the surgeon(s) focus(es) exclusively on the surgical aspects of the procedure at the expense of monitoring the ECG screen (but no serious problems develop); this usually occurs when closing the sternum • Perfusion problems: air locks, poor visibility because of unsatisfactory blood aspiration
Postbypass (73)	• Positioning, tension, and instrument handing errors, communication errors, surgical tunnel vision, and equipment problems • Anesthetic problems: e.g., adjustment of ventilating parameters, not starting inotropic support and vasodilators at an appropriate time • Communication problems during hand-over to ICU • Lack of seniority during transfer or in the team admitting the patient to ICU • Absence of monitoring for an excessive period of time during transfer to the ICU

ABP, arterial blood pressure; BAS, balloon atrial septostomy; CAP, coronary artery pattern; ECG, electrocardiograph; ICU, intensive care unit; SaO_2, arterial oxygen saturation.

Source: de Leval et al. [17]. Reproduced with permission from Elsevier.

Communication in the operating room

A brief preoperative conversation between the anesthesiologist and surgeon is advisable before the patient is brought to the OR for induction of anesthesia. This is an informal "check-in" to communicate unique aspects of the case that affect anesthetic and surgical approaches, and can include issues such as planned sites of vascular access, (i.e. are two arterial lines needed for an aortic arch repair?); are there special plans for CPB such as regional cerebral perfusion; of the surgical options listed on the consent form which is most likely, risk of cardiac or vascular injury during re-entry sternotomy and plans for emergency bypass, high-risk induction of anesthesia and need for the surgeon to be present and CPB circuit primed and ready, and other details about the case that often are not decided until the patient has had a detailed preoperative examination and individual plan made. This conversation can be the day before, or the morning of, surgery, and ensures that concerns about the case are communicated beforehand, and not only at the time of surgical timeout (see below) so that preparations can be made before entering the operating room. This conversation can help avoid unexpected requests or procedures that are only known during, or even after, the surgical timeout.

Surgical safety checklist

The effectiveness of a surgical safety checklist (SSCL) gained wide recognition after Gawande and colleagues conducted a study of eight hospitals in diverse settings and populations that instituted a process that required a pre-induction checklist of patient identification, basic monitors, surgical and anesthetic factors; a time out before surgical incision introducing the team and role, re-identifying the patient, and reviewing surgical and anesthetic procedures; and a sign out before the patient leaves the operating room reviewing sponge and instrument counts, disposition of the patient, and whether any concerns were identified [18]. Surgical mortality and complications were recorded in 3,733 patients before the institution of the SSCL, and in 3,955 after its introduction, and mortality decreased from 1.5% before to 0.8% after ($p = 0.003$), and inpatient complications decreased from 11.0 to 7.0% ($p < 0.001$). At TCH, the SSCL was introduced in 2009 and has gone through a number of iterations for various operating rooms and types of cases in the institution. The current version for cardiac surgery cases with bypass is displayed in Figure 4.10. Institutional lessons learned in the evolution of the approach are numerous, perhaps most important that during each phase of the SSCL, all other activity is ceased and all involved are completely attentive to the checklist, and the checklist is read like a script and not recited from memory.

The preoperative briefing is initiated by the anesthesiologist and involves the anesthesia team, circulating nurse, patient, and parents and the parents are encouraged to listen and ask questions. Any questions are resolved, and the patient proceeds immediately to the operating room. The surgical timeout is initiated by the surgeon and occurs with the patient prepared and draped, and all surgical personnel scrubbed and in position for the operation, immediately before the incision. A crucial point is that all other activity is ceased, any extraneous noise such as music is silenced, and all in the operating room introduce themselves. If the patient needs attention due to instability the timeout is delayed.

Texas Children's Hospital Surgical Safety Checklist - CVOR: PERFUSIONIST PRESENT (VERSION 7.6)

Before transport to OR	Before skin incision	Before patient leaves the OR
BRIEFING (Holding or Inpatient Bed)	**TIMEOUT (Operating Room)**	**DEBRIEFING (Operating Room)**
BRIEFING MAY NOT BEGIN UNTIL AT LEAST ONE OF THE FOLLOWING IS COMPLETE: □ SURGEON PRESENT (PREFERRED) □ SURGEON BRIEFING DOCUMENT COMPLETE □ CIRCULATOR *AND* ANESTHESIOLOGIST HAVE DISCUSSED CASE WITH SURGEON (Implants available & Sterile, Equipment, Blood, etc)	**STOP** *ALL ACTIVITY IS SUSPENDED & MUSIC SILENCED* *NEW SURGEON / PROCEDURE- REPEAT TIMEOUT * **SURGEON: *INITIATES TIMEOUT*** □ ALL TEAM MEMBERS INTRODUCE THEMSELVES BY NAME & ROLE OR TEAM CONFIRMS NO CHANGES FROM PREVIOUS CASE	**SURGEON: *INITIATES DEBRIEFING AND CONFIRMS WITH SURGEON & ANESTHESIOLOGIST*** □ RECORDS NAME OF PROCEDURE □ CIRCULATOR VERBALIZES INSTRUMENT / SPONGE / NEEDLE COUNT RESULTS □ SURGEON VERBALLY ACKNOWLEDGES COUNT □ ALL SPECIMENS IDENTIFIED & LABELED □ SURGEON & ANESTHESIOLOGIST AGREE ON ESTIMATED BLOOD LOSS □ SURGEON, NURSE, SCRUB PERSON & ANESTHESIOLOGIST REVIEW KEY CONCERNS FOR RECOVERY & MANAGEMENT, PATIENT DISPOSITION □ WERE THERE ANY EVENTS THAT NEED REPORTING? □ SURGEON RECORDS PROCEDURE & POST OP POST OP DIAGNOSIS IN EPIC □ SURGEON COMPLETES POST OP NOTE □ CIRCULATOR IMPORTS SURGEON'S OP NOTE FROM ODWA TO EPIC
ANESTHESIOLOGIST: *INITIATES BRIEFING WHILE CIRCULATOR CONFIRMS WITH RECORD AND PARENT* □ CONFIRM CORRECT CHECKLIST FOR CASE □ PATIENT NAME VERIFIED WITH ARMBAND □ SURGEON NAME VERIFIED □ PROCEDURE VERIFIED WITH H&P OR PRE-OP NOTE *AND* CONSENT □ SITE CORRECTLY MARKED AND VERIFIED WITH CONSENT, UNLESS EXEMPT □ NPO STATUS KNOWN □ ALLERGY STATUS DISCUSSED □ AIRWAY STATUS IS KNOWN □ BLOOD LOSS RISK IS KNOWN □ BLOOD IS AVAILABLE OR IN PROCESS, IF NEEDED □ PRESENCE & AVAILABILITY OF DESIGNATED PRODUCTS IS VERIFIED WITH PARENT & BLOOD BANK □ BLOOD CONSENT VERIFIED □ AVAILABILITY & PRESENCE OF REQUESTED IMPLANTS, SUPPLIES & EQUIPMENT BASED ON SURGEON'S BRIEFING FORM CONFIRMED □ HAVE RECENT LABS BEEN REVIEWED?	**ANESTHESIOLOGIST: Verbalizes** □ PROPHYLACTIC ANTIBIOTICS GIVEN ON TIME, IF APPLICABLE □ LINE ACCESS/PLACEMENT □ ALLERGY STATUS CONFIRMED □ CONCERNS OR ANTICIPATED CRITICAL EVENTS (MEDICATION/ HISTORY/ INDUCTION/ AIRWAY) **PERFUSIONIST: Verbalizes** □ DONOR DESIGNATED BLOOD/ BLOOD PRODUCTS/ BLOOD TYPE □ CIRCUIT SIZE/ BYPASS PRIME TYPE □ CANNULAS/ REDO EQUIPMENT □ OTHER BYPASS CONSIDERATIONS OR CONCERNS □ CELL SAVER NEEDED (YES OR NO) **SCRUB PERSON: Verbalizes** □ INSTRUMENT & IMPLANT STERILITY CONFIRMED □ MEDICATIONS & SOLUTIONS ON FIELD LABELED **CIRCULATOR: Verbalizes** □ FIRE RISK ASSESSMENT DISCUSSED □ DEVICES/EQUIPMENT/IMPLANTS CONFIRMED, IF NEEDED □ FLUIDS FOR SPECIAL IRRIGATION AVAILABLE	***REGULATORY REQUIREMENT*** ***TRANSFER TO NEXT LEVEL OF CARE SHOULD NOT OCCUR UNTIL BRIEF/OPERATIVE NOTE COMPLETE*** Texas Children's Hospital®
ANESTHESIOLOGIST: ASKS: ANY CONCERNS? AGREE? ALL MUST VERBALIZE AGREEMENT INCLUDING FAMILY ***TEAM AND PATIENT PROCEED IMMEDIATELY TO OR***	**STOP** **SURGEON ASKS: ANY CONCERNS? AGREE? (ALL MUST VERBALIZE AGREEMENT)**	© Copyright 2018 Texas Children's Hospital

Figure 4.10 Texas Children's Hospital surgical safety checklist for cardiac surgery cases with bypass.

All personnel in the room, including the echocardiographers, all anesthesia personnel, any students or observers, are also part of the process. The timeout script is read so that no elements are missed, and any unexpected issues i.e. equipment or implant needs, are immediately addressed so they are ready when needed. Only when the checklist is completed, and the surgeon has asked about any concerns and any questions are resolved, does the operation commence. The SSCL, and particularly the surgical timeout, are observed and graded by a neutral observer periodically for correct and complete process and these data are reported regularly in the quality improvement efforts of the Heart Center.

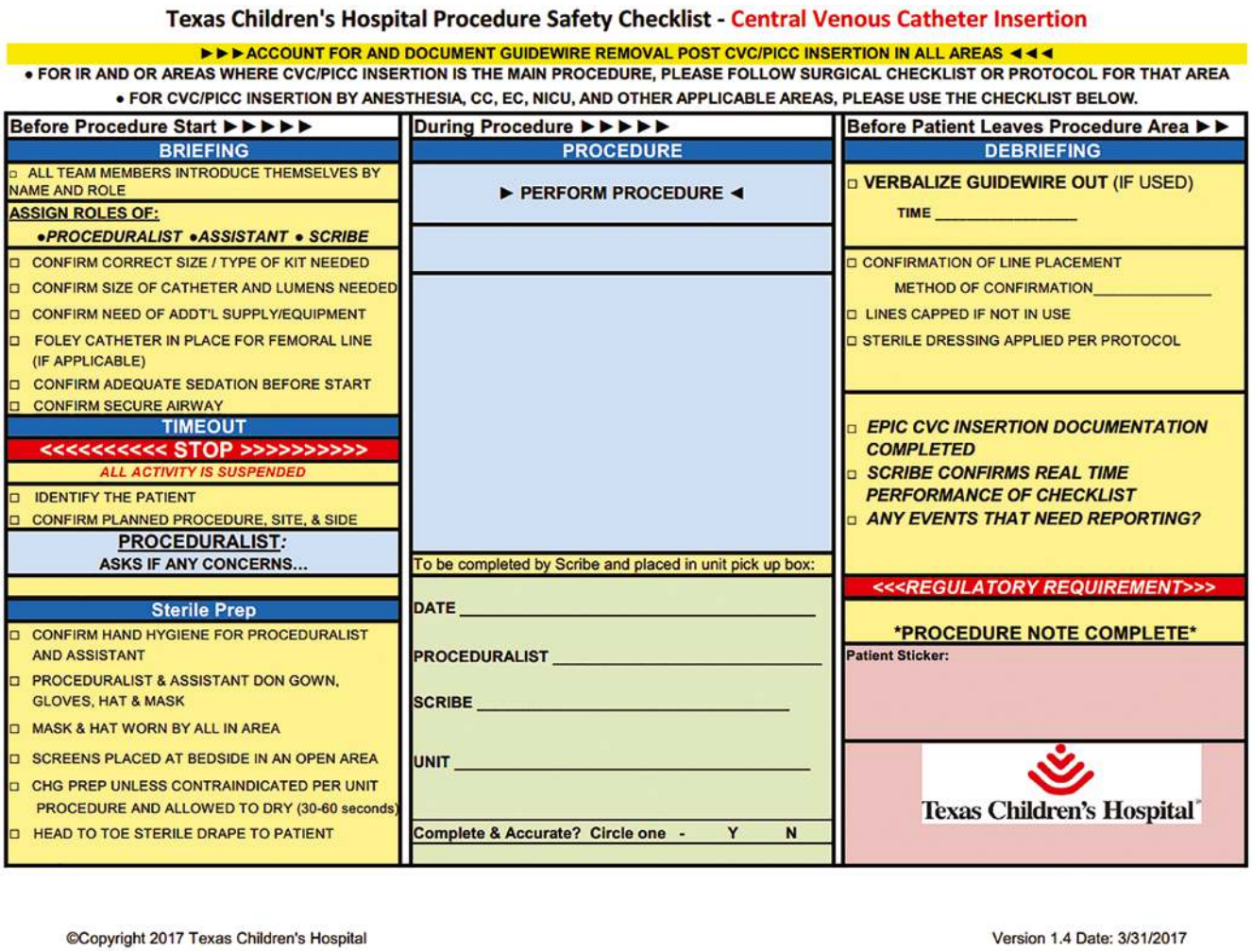
The surgical debriefing occurs in the OR after the attending surgeon has broken the scrub, and before the patient leaves the room; any issues or problems are verbalized, along with plans for disposition of the patient, i.e. extubation in the OR. The surgeon, anesthesiologist, and circulating nurse perform this activity in person.

Anesthesiology-specific checklists

The anesthesia team performs a number of complex procedures at the beginning of a cardiac surgical case; simultaneously managing the time pressure of starting the case and the often complex pathophysiology of an unstable patient. Distraction from best procedural practices is possible during this often intense period of anesthetic care. Central venous access is achieved by the anesthesiology team in nearly every cardiac surgical case, and in order to ensure best practices are followed for prevention of central line-associated bloodstream infection, and issues such as a retained guidewire, a checklist was introduced, to be reviewed once the anesthesiologist has scrubbed, gowned, gloved, and the patient is prepared and draped for the procedure (Figure 4.11). The anesthesiologist and the circulating nurse perform this checklist, and only when completed does line placement proceed. An important feature of the checklist is to announce when the central line guidewire has been removed, with the goal of preventing the rare but consequential complication of a retained guidewire.

Regional anesthesia is increasingly utilized in cardiac and thoracic surgical cases in congenital heart disease, and a checklist has been instituted to be completed before the procedure starts [19]. Of particular importance besides the site and laterally of the block or catheter, is the local anesthetic drug and dose, and any adjuvants such as opioids or alpha receptor agonists. A regional block may be performed by a team other than the primary anesthetic team, so this checklist is particularly important. Chapter 24 contains a detailed presentation of regional anesthesia techniques for congenital cardiac surgery.

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Texas Children's Hospital Procedure Safety Checklist - Central Venous Catheter Insertion

►►►ACCOUNT FOR AND DOCUMENT GUIDEWIRE REMOVAL POST CVC/PICC INSERTION IN ALL AREAS ◄◄◄

• FOR IR AND OR AREAS WHERE CVC/PICC INSERTION IS THE MAIN PROCEDURE, PLEASE FOLLOW SURGICAL CHECKLIST OR PROTOCOL FOR THAT AREA

• FOR CVC/PICC INSERTION BY ANESTHESIA, CC, EC, NICU, AND OTHER APPLICABLE AREAS, PLEASE USE THE CHECKLIST BELOW.

Before Procedure Start ►►►►►

BRIEFING

- ☐ ALL TEAM MEMBERS INTRODUCE THEMSELVES BY NAME AND ROLE

ASSIGN ROLES OF:

•PROCEDURALIST •ASSISTANT • SCRIBE

- ☐ CONFIRM CORRECT SIZE / TYPE OF KIT NEEDED
- ☐ CONFIRM SIZE OF CATHETER AND LUMENS NEEDED
- ☐ CONFIRM NEED OF ADDT'L SUPPLY/EQUIPMENT
- ☐ FOLEY CATHETER IN PLACE FOR FEMORAL LINE (IF APPLICABLE)
- ☐ CONFIRM ADEQUATE SEDATION BEFORE START
- ☐ CONFIRM SECURE AIRWAY

TIMEOUT

<<<<<<<<<< STOP >>>>>>>>>>

ALL ACTIVITY IS SUSPENDED

- ☐ IDENTIFY THE PATIENT
- ☐ CONFIRM PLANNED PROCEDURE, SITE, & SIDE

PROCEDURALIST:
ASKS IF ANY CONCERNS...

Sterile Prep

- ☐ CONFIRM HAND HYGIENE FOR PROCEDURALIST AND ASSISTANT
- ☐ PROCEDURALIST & ASSISTANT DON GOWN, GLOVES, HAT & MASK
- ☐ MASK & HAT WORN BY ALL IN AREA
- ☐ SCREENS PLACED AT BEDSIDE IN AN OPEN AREA
- ☐ CHG PREP UNLESS CONTRAINDICATED PER UNIT PROCEDURE AND ALLOWED TO DRY (30-60 seconds)
- ☐ HEAD TO TOE STERILE DRAPE TO PATIENT

During Procedure ►►►►►

PROCEDURE

► PERFORM PROCEDURE ◄

To be completed by Scribe and placed in unit pick up box:

DATE _____

PROCEDURALIST _____

SCRIBE _____

UNIT _____

Complete & Accurate? Circle one - Y N

Before Patient Leaves Procedure Area ►►

DEBRIEFING

- ☐ **VERBALIZE GUIDEWIRE OUT** (IF USED)

TIME _____

- ☐ CONFIRMATION OF LINE PLACEMENT

METHOD OF CONFIRMATION_____

- ☐ LINES CAPPED IF NOT IN USE
- ☐ STERILE DRESSING APPLIED PER PROTOCOL

- ☐ ***EPIC CVC INSERTION DOCUMENTATION COMPLETED***
- ☐ ***SCRIBE CONFIRMS REAL TIME PERFORMANCE OF CHECKLIST***
- ☐ ***ANY EVENTS THAT NEED REPORTING?***

<<<REGULATORY REQUIREMENT>>>

PROCEDURE NOTE COMPLETE

Patient Sticker:

Texas Children's Hospital

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Version 1.4 Date: 3/31/2017

Figure 4.11 Central venous catheter insertion checklist.

In the period after induction and before sterile preparation of the patient, many simultaneous procedures occur for patient positioning and padding, application of monitors such as backup pulse oximeter probes, near-infrared spectroscopy probes, defibrillation pads, and many others. To avoid the omission of any of these elements and the necessity to institute them after the patient is draped and interrupt the flow of the surgical case, a "Pre-Flight" anesthesia checklist was developed that was to be completed by the circulating nurse and anesthesiologist (Table 4.3).

Communication during the operation

Few procedures in medical practice are as complicated as congenital heart surgery, where the interdependence of surgical action, patient pathophysiology, anesthetic procedures, perfusion approaches, and surgical assistant and scrub personnel support depend on precise coordination and communication to achieve the goals of the operation, recognize and prevent adverse patient states, and rescue from such states, as they inevitably occur with significant frequency. The complexity of the surgical procedure flow demands consistent, clear communication, and omitting standardized elements of communication during cardiac surgery can lead to errors and adverse outcomes. With as many as 8–12 personnel directly involved in the care of the patient, consistency, protocols, and scripts are crucial, as well as a sense of when to communicate, and in what tone and frequency, i.e. anesthesiologist to the surgeon during periods of hypotension from surgical manipulation, and other events. For example, is the hypotension likely to be very short-lived and easily recoverable when retraction by the surgeon on the right ventricle for placement of inferior vena cava purse string sutures for cannulation stops? Or, is this a surgically-induced cardiac rhythm change resulting in hypotension that needs immediate action in the form of synchronized internal cardioversion? Congenital heart surgery cases each have a number of these moments, and the experience of the anesthesiologist with the surgical team will help determine the optimal frequency and level of communication, striking a balance between "needing to know" and changing the surgical flow, vs. "not needing to know" and keeping the flow of the surgery going. The intense concentration required by the surgeon argues for a quiet, calm operating room with minimal extraneous noise and conversation during the surgery. The concept of a "sterile cockpit," borrowed from the aviation industry, means that during safety-critical periods of the operation that unnecessary conversation is stopped,

Table 4.3 Texas Children's Hospital Cardiovascular Anesthesiology "Pre-Flight" Checklist

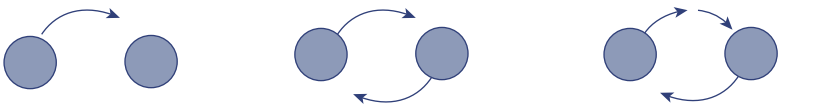
To be completed by circulating nurse and anesthesiologist immediately prior to patient preparation. The nurse asks the questions, anesthesiologist responds "Yes/No" (not indicated, or will correct now)

- Extremities, sacrum, and occiput positioned and padded properly?
- Vascular access connections and sites secure, padded, and lines are functioning?
- Five-lead ECG in place and functioning, displaying multiple leads?
- Two pulse oximeter probes in place and functioning?
- Extra backup pulse oximeter probes in place for infants?
- Blood pressure cuff in place and functioning on different extremity than an arterial line?
- Bilateral NIRS probes in place and functioning?
- Three temperature probes (nasopharyngeal, rectal, skin) in place, properly labeled, and functioning?
- TEE probe in place and not compressing oral structures?
- Urinary catheter secured and draining clear urine?
- Surgical rack (for drapes) in place and secure?
- Defibrillation pads, if indicated, in place, and connected to the defibrillator, with ECG synchronization leads in place and functioning?
- Electrocautery pad in place and connected to the unit?
- Forced-air warming blanket in place and functioning?
- Pacemaker box present and functioning?
- Adequate blood products in the operating room and checked?

NIRS, near-infrared spectroscopy; TEE, transesophageal echocardiography.

standardized terminology for communication is used, and instructions given by the surgeon are "read-back" when tasks are completed, i.e. heparin administered [20]. The idea of creating shared mental models among the disciplines in the cardiac operating room, to agree on critical points during the operation and methods of communication during these important junctures, can improve the quality and efficiency of information exchange [21].

van Wijngaarden and colleagues performed a video recording study of six coronary artery bypass graft (CABG) surgeries, and by personal interviews and focus group meetings with surgeons, anesthesiologists, and perfusionists, arrived at 64 items to be critical to communicate for safe CABG surgery [22]. These items were classified as to which subteams were involved, and type of communication, i.e. open loop, call-back, closed loop, and series (Figure 4.12); and exchange types classified by purpose (Table 4.4). Quality, consistency, frequency, timeliness, and appropriateness of communications were graded by viewing the videos, with the goal of developing a quality standard for the critical verbal exchanges between surgeons, anesthesiologists, and perfusionists. There was an average of 219 sequences of exchanges per operation, with the surgeon initiating 45%; perfusionist 33%, and anesthesiologist 21%. The most common types of exchanges were "status" – shared understanding of the current state; followed by "direction" – command an action to transition to a new state. Of the 64 critical events, on average 60 (94%) were consistently verbalized during the same phase of surgery. Quality of communication was graded as "substantive," e.g. specific information in a call back (e.g. "heparin is in" in response to "give heparin"), as opposed to insubstantive (e.g. "yes" or "OK" in response to "give heparin"). Substantive communication is less prone to error and was present in 40% of exchanges, instubstantive communication in 33%, and no call back (open loop communication not requiring a call back) in 27%. This study demonstrated that optimal high-quality communication could be improved and provided an important patient safety standard for intra-team communication during CABG operations.



Open-loop communication **Call-back communication** **Closed-loop communication**

	2 subteams		3 subteams	
Open loop	A	Protamine is at one third		
Call-back	S	Heprin may be administered	P	And the pump is empty
	A	Heparin administered	A	Yes
			S	Good
Closed loop	S	How much do you have [perfusionists]?	P	Breathing is also (...)?
			S	Yes sure
	P	About 100	A	Yes
	S	Oh, ok	P	Ok
Series	S	[anesthetist], should I stay here, because the pressure is 75	P	Off bypass
			A	Yes, I heard you
	A	Stay there?	S	Off bypass?
	S	At half a liter, or... Do you agree that it's going to fast/	A	Yes
			S	Wonderful
	A	No, fine, let's go off bypass (...)		
	S	Yes		

Figure 4.12 Loop types and examples per number of subteams involved. Open loops are exchanges without call-back and only involve one subteam. Call-backs are exchanges with call-backs from 1 or 2 subteams and in closed loops, the initiator fully "closes" the exchange loop with a final call after the receiver gave a call-back. Series involve more sequences between 2 or 3 subteams. A, anesthetist; P, perfusionist; S, surgeon. (Source: de Lind van Wijngaarden et al. [22] / Elsevier / CC BY 4.0.)

Table 4.4 List of critical events and critical subteam involved

Critical event	Critical subteams
Regulate anticoagulation	
Administer heparin	S+A
Heparin circulating	S+A
Heparin circulating 2 minutes,[a]	S+A
Activated clotting time (ACT) started	A+P
ACT is sufficient for cannulation (>300)/blue suction is on	S+P
ACT is sufficient for extracorporeal circulation (>400)	S+A+P
Cannulation	
Test suction	S+P
Suction is adequate	S+P
Divide the arterial and venous line	S+P
Prepare for cannulation	S+A+P
Arterial cannula has been inserted	S+A+P
Clamp removed from arterial cannula	S+P
Sufficient pulsation and line pressure	S+A+P
Permission to start retrograde autologous priming (RAP)	S+A+P
Start RAP[a]	S+A+P
RAP is complete[a]	A+P
Clamp removed from venous canule	S+P
Start extracorporeal circulation (ECC)	
Start ECC	S+A+P
Indicate ECC temperature	S+P
Full flow achieved	S+A+P
(Do not) adjust artificial breathing	S+A
Flush cardioplegia	
Flush cardioplegia	S+P
Stop flushing	S+P
Place aortic cross clamp	
Low flow[a]	S+A+P
Aortic cross clamp placed	S+A+P
Normal flow[a]	S+A+P
Administer cardioplegia	
Start cardioplegia	S+A+P
Pressure in root is adequate	S+P
Flow is adequate	S+P
Heart is still	S+A+P
Cardioplegia circulating for 2 minutes	S+P
Stop cardioplegia	S+P
Suck yellow	S+P
Last cardioplegia administered 15 minutes ago	S+A+P
Last cardioplegia administered 20 minutes ago	S+A+P
Remove aortic cross clamp	
Low flow[a]	S+A+P
Aortic cross clamp removed	S+A+P
Normal flow[a]	S+A+P
Stop ECC	
Continue artificial breathing[a]	S+A+P
Make output	S+A+P
Permission to reduce the flow	S+A+P
Artificial breathing is on	S+A+P
Heart rhythm is adequate	S+A+P
Heart function is adequate	S+A+P
Heart filling is adequate	S+A+P
The patient body temperature is adequate	S+A+P
Reduce flow/stop ECC	S+A+P
ECC at 1 L index	S+A+P
ECC at 1/2 L index	S+A+P
Stop ECC	S+A+P
Decannulation	
Administer protamine	S+A+P
Root needle removed	S+A+P
Venous cannula removed	S+A+P
Withdraw blood from the venous line	S+A+P
Protamine at 1/3	S+A+P
Stop blue suction	A+P
Blood volume left in the pump	S+A+P
Empty pump	S+A+P
Pomp is completely empty	S+A+P
Arterial cannulae removed	S+A+P
Protamine complete	S+A+P
Other events	
Table movements[a]	S+A+P
Hemodynamically compromising manipulation of the heart[a]	S+A+P
Sample taken from the anesthetic line during ECC[a]	S+A+P

A, anesthetic subteam, P, perfusion subteam; S, surgical subteam.

[a] Only if applicable.

Source: de Lind van Wijngaarden et al. [22] / Elsevier / CC BY 4.0.

Congenital heart surgery possesses many similarities to the events specified in this important study, but there are unique aspects such as different perfusion techniques (deep hypothermic circulatory arrest, regional cerebral perfusion) utilized more commonly in CHD; assessment of intracardiac air by TEE before aortic unclamping; and others. Each institution should develop a consistent approach to communication that is specific to the procedures practiced locally. The potential for adverse clinical states is greater for congenital heart surgery, with complex anatomy and physiology, small patient sizes and equipment increasing the risk for cannula malposition impairing perfusion and venous return, and a smaller margin of error given increased metabolic rates and frequent arterial desaturation. The anesthesiologist, surgeon, and perfusionist, in particular, must work together to troubleshoot and communicate these abnormal states, for example, cerebral oxygen desaturation during bypass, and use a standardized system of clear communication to achieve these goals [23]. Particularly in a large system where there are multiple possible combinations of intraoperative personnel, a standardized approach to communication will minimize the risk of errors. Another crucial aspect of communication is that if any member of the team has a question, concern, or is uncertain about what was communicated or intended, they must speak up for clarification, for the benefit of the patient. This includes junior members of the team or those on the lower end of the authority gradient; i.e. a scrub technician with a concern or question directed at a senior surgeon. The concepts of psychological safety discussed

previously apply to the OR; senior physicians, in particular, must pay attention to including the contributions of all members of the team in a non-threatening manner, and voicing appreciation for their contribution to the optimal care of the patient. On the extreme end of the scale, the disruptive physician has severely detrimental effects on patient safety and should not be tolerated on the congenital heart surgery team [24].

In addition to the standardized approach to communication during surgery, at TCH the surgeon wears a lightweight, high-definition camera on their headlight that reproduces exactly what they are viewing, so that caregivers, and learners in the room but not directly involved in the surgical team, can see accurately what phase of the surgery is ongoing, and have a better understanding of the surgical procedure (Figure 4.13). This view is displayed on multiple high-definition monitors around the OR that produce a magnified image of the surgeon's field of view. The advantage of this system over a fixed, overhead camera integrated into a surgical light source is the exact view that changes with the surgeon's position, and is not obscured by the surgical team itself. Particularly important beneficiaries of this system are the perfusionist and the anesthesiologist.

Communication during emergencies

During congenital heart surgery, emergencies occur with some regularity that, while not unexpected, can catch the unprepared team off guard and lead to a disorganized or delayed response that can increase patient risk and result in adverse outcomes. One such event is massive bleeding during re-entry sternotomy requiring an emergency institution of CPB. For higher-risk patients, i.e. aortic position immediately behind and adjacent to the sternum, preparations such as the site of emergency cannulation, selection of emergency cannulas, assessment of femoral vessels preoperatively by ultrasound or other imaging, are crucially important. When the actual emergency occurs, it is also important to institute an approach consistent with the "sterile cockpit," as noted above. The surgeon takes over communication, gives clear instructions which are read back and carried out, all extraneous noise and activity stops, and the entire team focuses on resuscitating the patient, instituting bypass as quickly as possible, and controlling the source of the bleeding. Development of protocols, and simulation scenarios of the emergent institution of CPB, especially for new team members, can facilitate team performance during actual emergencies [25, 26]. Cognitive aids can also facilitate team performance during sudden unexpected emergencies, to ensure that all necessary steps are carried out; one such cognitive aid has been developed for massive systemic air embolism on bypass [27] (Figure 4.14).

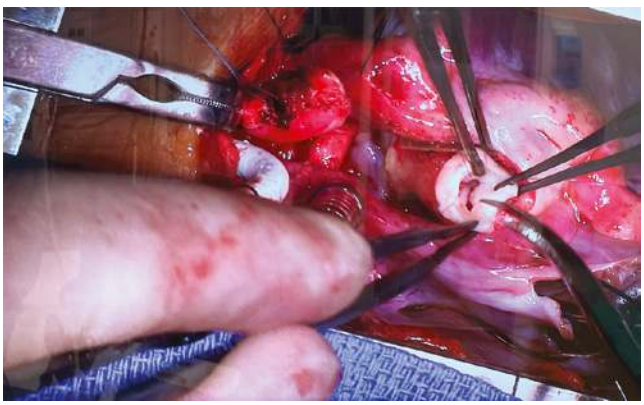


Figure 4.13 View from the surgeon's headlight camera displaying a high-definition magnified image of repair of supravalvar aortic stenosis. The aorta has been transected and the sinuses of Valsalva are being incised to prepare for autologous pericardial patch augmentation. The aortic cross clamp is seen at the upper lefthand corner of the screen; just below it is the white-colored polytetrafluoroethylene graft sewn to the innominate artery for arterial cannulation.

Other intraoperative multidisciplinary collaborations

Variation in clinical care paradigms, either within an institution or between institutions, are very significant and there is increasing evidence that a standardized approach to similar clinical situations can improve outcomes and control costs of medical care. One such approach is the protocols for early tracheal extubation after congenital heart surgery, i.e. in the operating room or within 6 hours of ICU admission. The Collaborative Learning Project developed a clinical practice guideline for two common lesions, coarctation of the aorta and tetralogy of Fallot repair, among 10 congenital cardiac surgery programs in the Pediatric Heart Network of the U.S. National Heart, Lung, and Blood Institute (NHLBI) [28]. This guideline was developed using collaborative learning techniques that included site visits, and a number of meetings among the multidisciplinary investigators to develop approaches to decrease the time to tracheal extubation using the Delphi method. The principles of anesthetic care included limiting intraoperative opioid (fentanyl) to no more than 10 mcg/kg/hour of surgery; utilizing dexmedetomidine from the beginning of the anesthetic, and utilizing adjunct pain control techniques such as acetaminophen, and regional anesthesia where applicable (Table 4.5 for the TCH approach). Five sites actively instituted this protocol, and five did not change their usual standard of care. The rate of early extubation increased in the active sites from 11.7 to 66.9% ($p < 0.001$) with no change in the reintubation rate. The median duration of postoperative ventilation among active sites decreased from 21.2 to 4.5 hours ($p < 0.001$). The control sites experienced no significant change in these parameters. Implementation of the protocol was also associated with a significant decrease in intraoperative opioid and benzodiazepine dosages, with no change in volatile agent exposure. Intraoperative dexmedetomidine usage increased, and postoperatively there was a decrease in opioid, benzodiazepine, dexmedetomidine, and ketorolac dosages [29]. In addition to intraoperative protocols, training and communication to ICU nursing and physician staff are critically important when instituting early extubation protocols so that these staff are prepared to assess and support the airway of the extubated patient they receive from the OR, and intentionally make

AL Grawany

2. Systemic Air Embolism

Arterial Line–On Pump

ACTIONS

1. First witness states loud & clear "MASSIVE AIR EMBOLISM EMERGENCY"
   - *A. Ask: "Who will be the crisis manager?"*
   - *B. VOCERA page back-up perfusionist*
   - *C. VOCERA page Attending Anesthesia*
   - *D. Start crisis timer*
2. STOP cardiopulmonary bypass immediately
3. Clamp *Arterial line near cannulation* immediately (*to prevent additional air entry*)

1. ANESTHESIOLOGIST: Place patient in steep Trendelenberg
2. ANESTHESIOLOGIST: Ventilate lungs with 100% FiO2
3. Locate, Confirm, and Control source of air
4. Re-prime Lines
   - Purge air from arterial line (aspirate of refill line)
5. Start CPB and Consider Retrograde Cerebral Perfusion
6. Cool patient on CPB to 25°C, Pack head in ice (30–40 min)
7. If needed, vasopressors to raise perfusion pressure (50–70 mmHg)
8. Complete planned operation
9. Slowly rewarm to 35° C
10. Consider Hyperbaric Oxygen Therapy

DRUG DOSES

Mannitol: 1g/kg IV

Methylprednisolone: 30 mg/kg IV

Dexamethasone: 20 mg IV x1

Retrograde Cerebral Perfusion

1. Purge air and refill CPB arterial line
2. SURGEON: Place retrograde cardioplegia cannula into SVC or insert arterial cannula into SVC
   if bicaval cannulation, connect arterial line to seared SVC cannula
3. Begin retrograde Perfusion with 20°C hypothermia at 1–2 L/min for 1–3 min
   Include period with carotid compression to clear vertebral system
4. Maintain perfusion pressure < 25 mmHg

Sources of Air Emboli

- Surgical [operative] Air
- Pump Circuit (check arterial line, reservoir, cardioplegia delivery system)
- Anesthesia Arterial Line

Figure 4.14 Crisis checklist developed for systemic air embolism while on cardiopulmonary bypass. Troubleshooting directives are on the right, crisis protocol is on the left. (Source: Tarola et al. [27]. Reproduced with permission from IEEE.)

Table 4.5 Texas Children's Hospital Heart Center approach to operating room extubation

Preoperatively:
- Patient at least 3 months old
- Surgery STAT category 1–3
- No preoperative respiratory support or difficult airway
- Stable hemodynamic status not receiving continuous inotropic support

Intraoperative:
- Opioids: limit to no more than 20–25 mcg/kg fentanyl; add incremental morphine 0.025 mg/kg per dose if needed at end of surgery
- Dexmedetomidine 0.5–0.7 mcg/kg/hour started at beginning of anesthetic, ±loading dose
- Volatile anesthetic agent: any agent at any MAC level required for anesthesia/hemodynamic stability
- Benzodiazepines: small doses as premedication/or during bypass only
- Intravenous acetaminophen 15 mg/kg, maximum dose 1,000 mg, post-bypass
- Ondansetron 0.1 mg/kg, maximum dose 4 mg, post-bypass
- Regional anesthesia/catheter at beginning of the case, or local anesthetic wound infiltration at end of the case whenever possible
- Order patient/nurse controlled morphine analgesia in the operating room and bring to ICU bedside
- Stable hemodynamics on minimal vasoactive support; no significant pulmonary hypertension
- No significant bleeding, ACT at or below baseline
- Favorable respiratory mechanics: low ventilating pressures including PEEP, minimal A-a gradient if acyanotic, PaO_2>40 mm Hg on low FiO_2 if cyanotic lesion

Table 4.5 (Continued)

- Full reversal of neuromuscular blockade with sugammadex 4 mg/kg
- The oral airway in place
- Extubation in the OR when adequate spontaneous respiratory rate/tidal volumes achieved with no pressure support ventilation
- Goal: "sedated" extubation with zero end-tidal volatile agent
- Adequate observation time to ensure stable airway; prepared to treat upper airway obstruction/laryngospasm

Intensive care unit:
- Transport to ICU with Jackson-Rees circuit and 100% oxygen by anesthesia facemask to closely monitor ventilation
- Close attention to airway obstruction and ventilation by anesthesia team immediately after arrival to ICU
- Review first ABG and chest radiograph in ICU
- Patient/nurse-controlled morphine analgesia

Abbreviations: A-a, alveolar-to-arterial gradient; ABG, arterial blood gas; ACT, activated clotting time; MAC, minimum alveolar concentration; PEEP, positive end-expiratory pressure; STAT, Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery Risk Category Score.

progress toward early extubation, when the patient is ready no matter what the timing. This approach is consistently applied at TCH, where in the past 4 years, 32% of patients are extubated in the operating room after cardiac surgery [30] (Table 4.6). Additional information about early extubation is discussed in Chapter 24.

Complex congenital cardiac operations consistently have a high rate of significant post-bypass bleeding, and

Table 4.6 Operating room extubations after cardiac surgery at Texas Children's Hospital 2017–2020

Age group	Percent extubated in the operating room, TCH (Number of patients extubated, % of age group)	Percent extubated in the operating room, STS-CCAS database, *N* = 118 programs
Neonates, 0–30 days	0	4%
Infants, 1–12 months	76 (9%)	19%
Children, 1–17 years	669 (60%)	49%
Adults, >18 years	59 (49%)	37%
Cardiac lesion		
ASD closure	97 (85%)	64%
VSD closure	129 (48%)	34%
Tetralogy of Fallot repair	18 (15%)	21%
Atrioventricular canal repair (partial, intermediate and complete)	31 (26%)	13%
Bidirectional cavopulmonary connection	8 (5%)	31%
Fontan operation	142 (92%)	52%
Norwood stage I palliation	0	0
All procedures	32%, *N* = 2,867 procedures	22%, *N* = 119,198 procedures

All procedures include bypass and non-bypass cardiac cases. ASD, atrial septal defect; CPB, cardiopulmonary bypass; STS-CCAS, Society of Thoracic Surgeons' Congenital Heart Surgery, and Congenital Cardiac Anesthesia Society Database; TCH, Texas Children's Hospital; VSD, ventricular septal defect.
[a] In OR, extubation is defined as extubation by the primary anesthesia team either in the OR or immediately upon arrival in the ICU by the anesthesia team without utilizing an ICU ventilator
Source: Data courtesy of David F. Vener, M.D [30].

hypofibrinogenemia is a common cause, especially in neonates and small infants. Cryoprecipitate is frequently utilized in these situations and is often ordered and thawed in advance in anticipation of acute need; but if not needed the unit is wasted, resulting in significant cost to the patient and institution. At Texas Children's Hospital, a multidisciplinary team consisting of anesthesiologists, blood bank coagulation specialists, surgeons, and nurses devised a standardized pathway utilizing rotational thromboelastometry during rewarming on CPB to help anticipate the need for fibrinogen. If indicated and the patient is less than 5 kg; 1–2 units of cryoprecipitate are ordered and thawed. If the patient is greater than 5 kg in weight, then lyophilized fibrinogen (Riastap®) is utilized. The institution of this protocol resulted in the reduction of wastage of cryoprecipitate by 61%, from 37 units/month in the year prior to the protocol, to 14 units/month in the first 5 months of the protocol [31] (Figure 4.15). See Chapter 16 for further discussion of bleeding and coagulation.

Intensive care unit handoffs

Transfer of care from the OR team to the ICU team after congenital heart surgery can be a time of intense activity, with multiple caregivers from a number of disciplines including nursing, respiratory therapy, surgery, anesthesia, intensive care, and involving all of their trainees and advanced practice providers (APP). At times there can be as many as 10–12 caregivers at the bedside in the immediate postoperative period. This can be a time of patient instability, and the interruption in monitoring that occurs can mask a destabilizing state. Delays in the communication of handoff information while the OR team stabilizes the patient can hamper the ability of the ICU team to provide fully informed care. Structured, consistent, clear, and scripted handoffs from the OR to ICU teams, and in many other healthcare settings, reduce technical and informational errors and lead to improved caregiver confidence and satisfaction when assuming care for a complex patient [32, 33].

TCH Heart Center implemented a structured handoff process over 20 years ago, which has been through a number of iterations and is now a standardized, process where the expected elements of communication are communicated in a consistent, efficient approach. The receiving ICU team consists of two bedside nurses, a respiratory therapist, and the ICU attending and fellow/APP. The patient is transported from the OR to ICU by the anesthesia team, surgical fellow, and circulating nurse, fully monitored with emergency drugs, volume expanders, and emergency airway equipment at hand. Upon arrival, and with the anesthesiologist's permission after ascertaining that the patient is stable, the physiologic monitoring module is transferred from the transport monitor to the ICU monitor, a process that results in loss of monitoring for 10–15 seconds. Once this occurs, the respiratory therapist connects the ventilator with the anesthesiologist's specified settings, and adequate ventilation is ascertained by auscultation, observation of chest rise, and ventilator parameters. Then, initial arterial blood gas and other admission laboratory studies are drawn. Vasoactive and sedative infusions are quickly reviewed and double-checked by the nursing and anesthesia teams. Then the handoff begins after ensuring that all necessary personnel are present, and the

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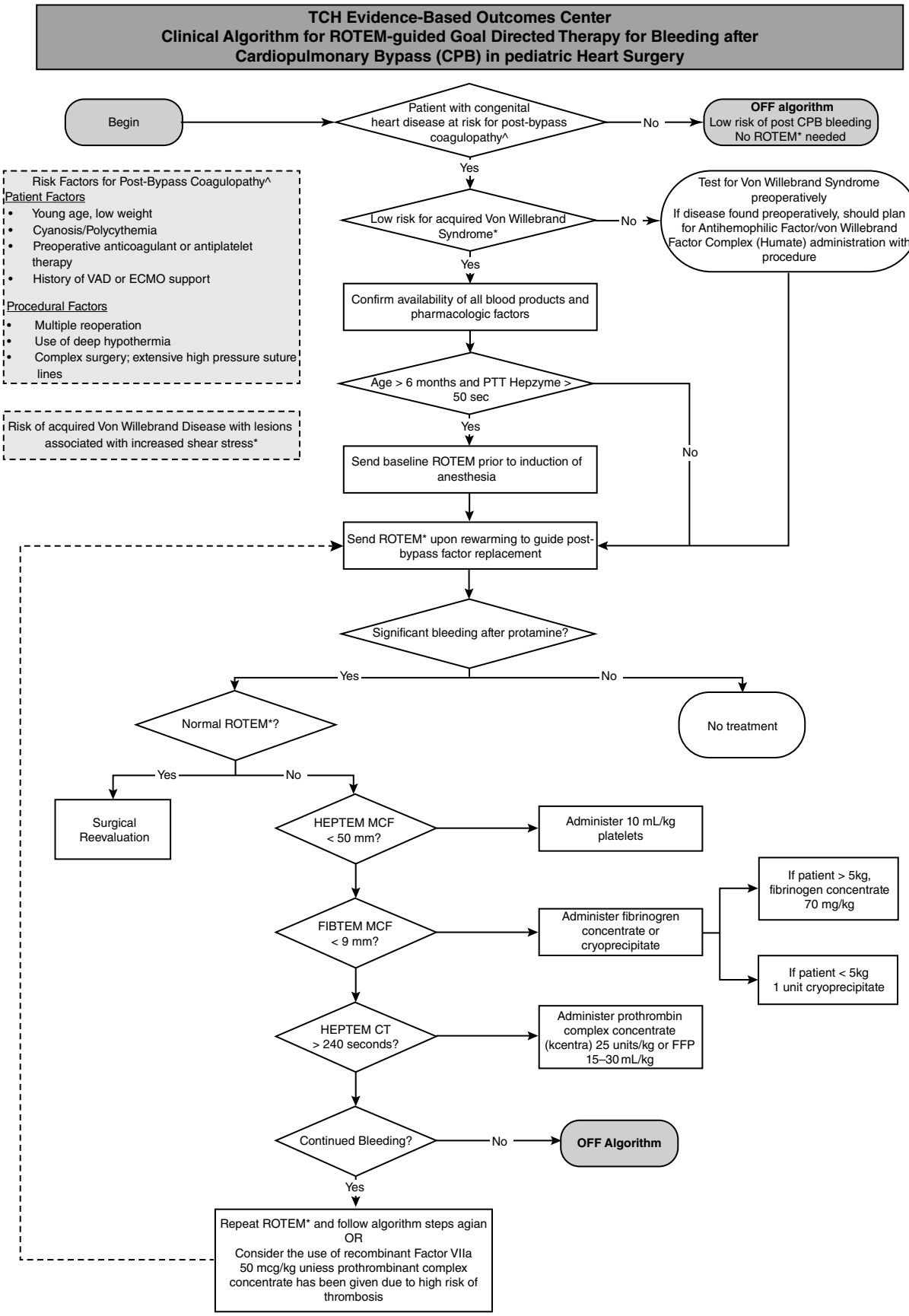


Figure 4.15 Rotational thromboelastometry (ROTEM®) guided goal-directed therapy algorithm for bleeding after cardiopulmonary bypass. CT, clotting time; ECMO, extracorporeal membrane oxygenation; FIBTEM, fibrinogen thromboelastometry; HEPTEM, heparin thromboelastometry MCF, maximum clot firmness; VAD, ventricular assist device.

nursing staff can devote their full attention. All activity in the room except direct patient care ceases, and all other conversations are silenced, much like the surgical time out, and the structured handoff process begins. First, the attending surgeon briefly introduces the patient's pertinent demographic details, past surgical history, and preoperative anatomic and physiologic state. Then, s/he details the surgery performed including any change in surgical plan or unexpected findings. Any issues with bypass, or significant issues like bleeding or treatment of arrhythmias, are reviewed. The postoperative echocardiogram is summarized and desired plans for extubation and hemodynamic goals are communicated. Next, the anesthesiologist reports on preoperative medications and allergies and briefly summarizes the induction of anesthesia, any airway issues, and the pre-bypass course. Bypass and aortic cross-clamp times, as well as any CPB issues including neuromonitoring, are communicated. Weaning and post bypass periods are summarized as well as inotropic and vasoactive support, anesthetic drug doses, and blood product administration, as well as adequate filling pressures and systemic blood pressure, current cardiac rate and rhythm including the need for temporary pacing. Arterial blood gases and ventilatory status, as well as last time of administration of antibiotics, and opioids/sedatives/neuromuscular blockade reversal are reviewed. Any problems or unexpected events are communicated. A review of endotracheal tube size and position, central and arterial lines, mediastinal drains, transthoracic lines, and pacemaker wires, along with urine output and bleeding assessment completes the information transfer. Hemodynamic goals and plans for extubation or other therapies are then discussed among the surgical, anesthesia, ICU, and nursing teams. Inventory of blood products available at the bedside is reviewed. Questions are elicited and answered to complete the report. After the transfer of information, the ICU attending physician requests a summary of the immediate postoperative plans from their fellow/APP, and the primary bedside nurse also voices their understanding of the postoperative plans. Finally, the postoperative chest radiograph is performed and reviewed by the team, along with the first arterial blood gas, hematocrit, lactate, and electrolytes. When all are satisfied with the status of the patient and the handoff of information, the care is formally transferred to the ICU team. The handoff process is summarized in Table 4.7. The entire handoff process usually requires no more than 10 minutes, and of necessity must be this efficient in a busy CICU where the team has many other patients and responsibilities, including at times several patients arriving from the ORs at short intervals. See Chapter 36 for an extensive presentation of CICU care.

Table 4.7 Texas Children's Hospital cardiac operating room to cardiac intensive care unit handoff procedure

1. After transfer of physiologic monitors, connection to the ventilator, and blood draw for ABG, electrolytes, hematocrit, lactate, all personnel cease conversation and unnecessary activity to participate in the handoff process
2. Attending surgeon verbal report:
   - Brief demographics, past surgical history, preoperative anatomic/physiologic status
   - Details of surgery, including any change in plans or unexpected findings
   - Issues with bypass, hemodynamics, bleeding, other problems
   - Postoperative echocardiogram
   - Hemodynamic goals and plans for extubation
3. Attending anesthesiologist verbal report:
   - Preoperative concurrent medical problems, medications, allergies
   - Induction of anesthesia including any airway problems
   - Pre-bypass course
   - Bypass period: bypass duration, aortic cross-clamp duration, lowest temperature, special techniques such as regional cerebral perfusion, neuromonitoring
   - Bypass weaning and post-bypass period: inotropic/vasoactive support, ventilation parameters, bleeding and blood product administration, antifibrinolytic/factor administration, urine output
   - Hemodynamics: optimal heart rate, systemic arterial pressure, central venous/right and left atrial pressures, cardiac rhythm/arrhythmias, temporary pacing
   - Anesthetic/sedative doses including last doses, muscle relaxation and reversal, time of the last dose of antibiotics
   - Unexpected events or problems
   - Review of support lines/tubes: endotracheal tube size, depth, cuff; vascular access: arterial/central/transthoracic/peripheral catheters – size, site, lumens; pacing wires, mediastinal/pleural drains, peritoneal dialysis catheter, urinary catheter
   - Inventory of blood products/volume expanders available at the bedside
4. Attending intensivist verbal report:
   - Brief readback of the patient status
   - Summary of early postoperative plans for sedation/analgesia, extubation, hemodynamic goals, bleeding
5. Bedside nurse verbal report:
   - Reads back early postoperative plans for sedation/analgesia, extubation, hemodynamic goals, bleeding
6. Questions/clarifications: any caregiver
7. Chest radiograph, ABG/lab results: all review and order necessary adjustments
8. The formal handover of care to ICU team

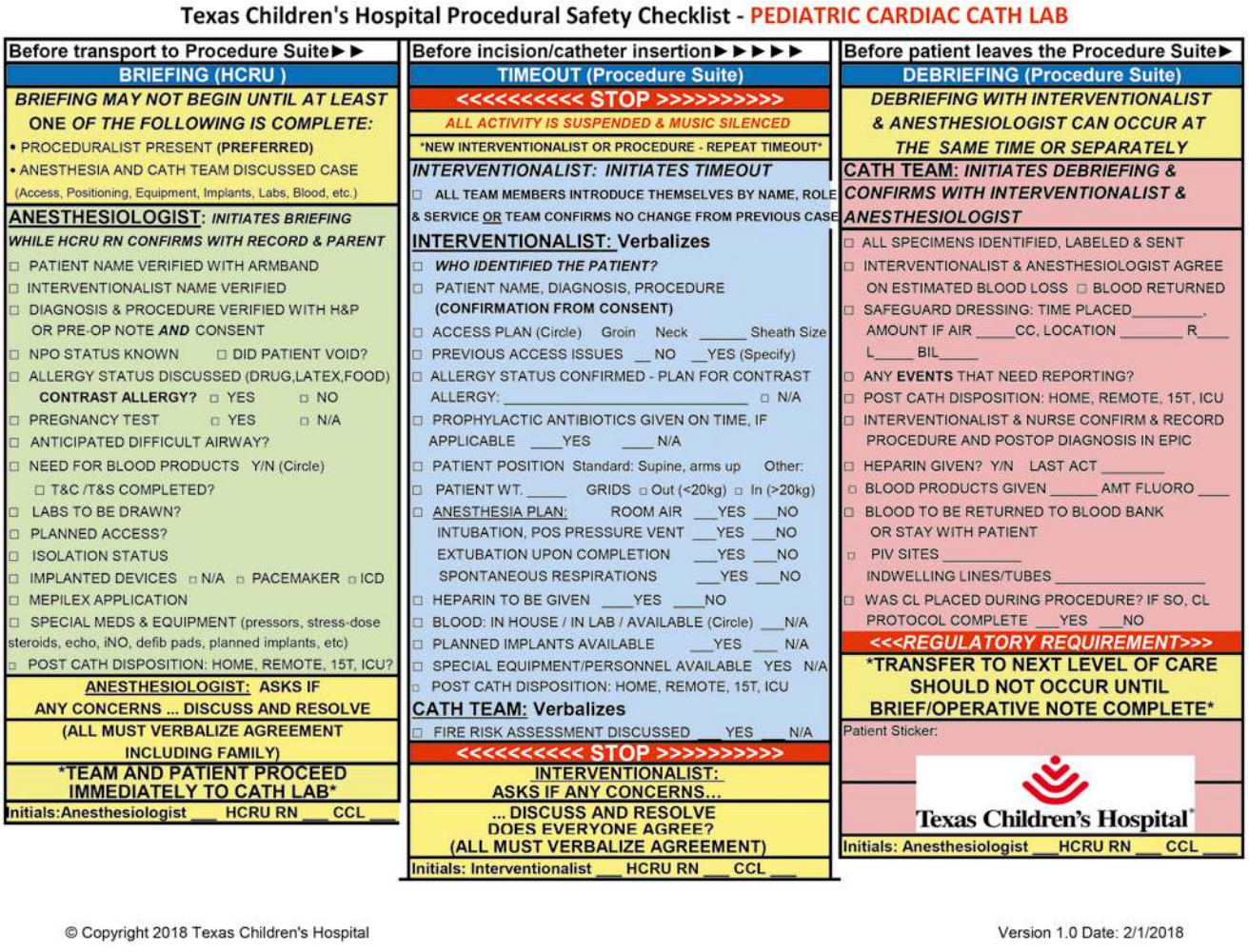
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The cardiac catheterization laboratory

The modern cardiac catheterization laboratory (CCL) shares a number of teamwork and communication aspects with the cardiac operating room. The risk of patient instability, need for resuscitation, and adverse outcomes increase with younger age and smaller size of the patient, and complexity of the cardiac anatomy and pathophysiology. The degree of invasiveness of the catheter procedure also correlates with risk to the patient, with procedures such as PDA stent or occlusion in small infants, stenting of the right ventricular outflow tract, balloon dilation of aortic stenosis in infants, pulmonary vein interventions, and pulmonary hypertension studies some of the clinical scenarios conferring the highest risk [3]. In these patients, a preoperative discussion with the interventionalist, and plans for surgical backup, i.e. ECMO if indicated, must be made early, and scheduled appropriately so that the requisite equipment and personnel are available. At Texas Children's Hospital, the Catheterization Safety Checklist has been developed and is closely similar to the SSCL (Figure 4.16). The pre-catheterization timeout is performed before starting the procedure, to ensure that all are aware of the plans for the procedure. Communication among the interventionalist, anesthesiologist, and nursing teams is not usually as frequent or intense as in the cardiac OR, but the same principles of clear, standardized, consistent communication, with readback as necessary, apply. Especially important are the issues of which the team is giving common medications, i.e. heparin, drugs to elicit arrhythmias, etc. Emergency drugs and defibrillation/cardioversion capability must be in the room, with equipment tested regularly for proper function. Chapter 34 presents a detailed discussion of cardiac catheterization anesthesia management.

Enhanced recovery after cardiac surgery

Enhanced Recovery After Surgery (ERAS) programs are multidisciplinary collaborations designed to standardize the approach to patient care for a particular surgery or related surgeries, enhance preoperative preparation and education, intraoperative standardization, and postoperative approach to pain control, early mobility and nutrition, and preventing complications to allow earlier discharge and return to baseline normal activities of daily living. In adult surgery, ERAS programs for colorectal surgery are among the most detailed and advanced, and there is significant evidence that consistent application of such guidelines does



Texas Children's Hospital Procedural Safety Checklist - PEDIATRIC CARDIAC CATH LAB

Before transport to Procedure Suite►►

BRIEFING (HCRU)

BRIEFING MAY NOT BEGIN UNTIL AT LEAST ONE OF THE FOLLOWING IS COMPLETE:

- PROCEDURALIST PRESENT **(PREFERRED)**
- ANESTHESIA AND CATH TEAM DISCUSSED CASE (Access, Positioning, Equipment, Implants, Labs, Blood, etc.)

ANESTHESIOLOGIST: *INITIATES BRIEFING WHILE HCRU RN CONFIRMS WITH RECORD & PARENT*

- ☐ PATIENT NAME VERIFIED WITH ARMBAND
- ☐ INTERVENTIONALIST NAME VERIFIED
- ☐ DIAGNOSIS & PROCEDURE VERIFIED WITH H&P OR PRE-OP NOTE ***AND*** CONSENT
- ☐ NPO STATUS KNOWN ☐ DID PATIENT VOID?
- ☐ ALLERGY STATUS DISCUSSED (DRUG,LATEX,FOOD) **CONTRAST ALLERGY?** ☐ YES ☐ NO
- ☐ PREGNANCY TEST ☐ YES ☐ N/A
- ☐ ANTICIPATED DIFFICULT AIRWAY?
- ☐ NEED FOR BLOOD PRODUCTS Y/N (Circle) ☐ T&C /T&S COMPLETED?
- ☐ LABS TO BE DRAWN?
- ☐ PLANNED ACCESS?
- ☐ ISOLATION STATUS
- ☐ IMPLANTED DEVICES ☐ N/A ☐ PACEMAKER ☐ ICD
- ☐ MEPILEX APPLICATION
- ☐ SPECIAL MEDS & EQUIPMENT (pressors, stress-dose steroids, echo, iNO, defib pads, planned implants, etc)
- ☐ POST CATH DISPOSITION: HOME, REMOTE, 15T, ICU?

ANESTHESIOLOGIST: ASKS IF ANY CONCERNS ... DISCUSS AND RESOLVE

(ALL MUST VERBALIZE AGREEMENT INCLUDING FAMILY)

TEAM AND PATIENT PROCEED IMMEDIATELY TO CATH LAB

Initials:Anesthesiologist ___ HCRU RN ___ CCL ___

Before incision/catheter insertion►►►►►

TIMEOUT (Procedure Suite)

<<<<<<<<<< STOP >>>>>>>>>>

ALL ACTIVITY IS SUSPENDED & MUSIC SILENCED

NEW INTERVENTIONALIST OR PROCEDURE - REPEAT TIMEOUT

INTERVENTIONALIST: INITIATES TIMEOUT

- ☐ ALL TEAM MEMBERS INTRODUCE THEMSELVES BY NAME, ROLE & SERVICE OR TEAM CONFIRMS NO CHANGE FROM PREVIOUS CASE

INTERVENTIONALIST: Verbalizes

- ☐ ***WHO IDENTIFIED THE PATIENT?***
- ☐ PATIENT NAME, DIAGNOSIS, PROCEDURE **(CONFIRMATION FROM CONSENT)**
- ☐ ACCESS PLAN (Circle) Groin Neck _____ Sheath Size
- ☐ PREVIOUS ACCESS ISSUES __ NO __YES (Specify)
- ☐ ALLERGY STATUS CONFIRMED - PLAN FOR CONTRAST ALLERGY: _____ ☐ N/A
- ☐ PROPHYLACTIC ANTIBIOTICS GIVEN ON TIME, IF APPLICABLE ____YES ____ N/A
- ☐ PATIENT POSITION Standard: Supine, arms up Other:
- ☐ PATIENT WT. _____ GRIDS ☐ Out (<20kg) ☐ In (>20kg)
- ☐ ANESTHESIA PLAN: ROOM AIR ___YES ___NO
  INTUBATION, POS PRESSURE VENT ___YES ___NO
  EXTUBATION UPON COMPLETION ___YES ___NO
  SPONTANEOUS RESPIRATIONS ___YES ___NO
- ☐ HEPARIN TO BE GIVEN ____YES ____NO
- ☐ BLOOD: IN HOUSE / IN LAB / AVAILABLE (Circle) ___N/A
- ☐ PLANNED IMPLANTS AVAILABLE ___YES ___ N/A
- ☐ SPECIAL EQUIPMENT/PERSONNEL AVAILABLE YES N/A
- ☐ POST CATH DISPOSITION: HOME, REMOTE, 15T, ICU

CATH TEAM: Verbalizes

- ☐ FIRE RISK ASSESSMENT DISCUSSED ___YES ___N/A

<<<<<<<<<< STOP >>>>>>>>>>

INTERVENTIONALIST: ASKS IF ANY CONCERNS...

... DISCUSS AND RESOLVE DOES EVERYONE AGREE? (ALL MUST VERBALIZE AGREEMENT)

Initials: Interventionalist ___HCRU RN ___CCL ___

Before patient leaves the Procedure Suite►

DEBRIEFING (Procedure Suite)

DEBRIEFING WITH INTERVENTIONALIST & ANESTHESIOLOGIST CAN OCCUR AT THE SAME TIME OR SEPARATELY

CATH TEAM: ***INITIATES DEBRIEFING & CONFIRMS WITH INTERVENTIONALIST & ANESTHESIOLOGIST***

- ☐ ALL SPECIMENS IDENTIFIED, LABELED & SENT
- ☐ INTERVENTIONALIST & ANESTHESIOLOGIST AGREE ON ESTIMATED BLOOD LOSS ☐ BLOOD RETURNED
- ☐ SAFEGUARD DRESSING: TIME PLACED_____, AMOUNT IF AIR _____CC, LOCATION _____ R____ L_____ BIL_____
- ☐ ANY **EVENTS** THAT NEED REPORTING?
- ☐ POST CATH DISPOSITION: HOME, REMOTE, 15T, ICU
- ☐ INTERVENTIONALIST & NURSE CONFIRM & RECORD PROCEDURE AND POSTOP DIAGNOSIS IN EPIC
- ☐ HEPARIN GIVEN? Y/N LAST ACT _____
- ☐ BLOOD PRODUCTS GIVEN _____ AMT FLUORO ____
- ☐ BLOOD TO BE RETURNED TO BLOOD BANK OR STAY WITH PATIENT
- ☐ PIV SITES _____ INDWELLING LINES/TUBES _____
- ☐ WAS CL PLACED DURING PROCEDURE? IF SO, CL PROTOCOL COMPLETE ___YES ___NO

<<<REGULATORY REQUIREMENT>>>

TRANSFER TO NEXT LEVEL OF CARE SHOULD NOT OCCUR UNTIL BRIEF/OPERATIVE NOTE COMPLETE

Patient Sticker:

Texas Children's Hospital

Initials: Anesthesiologist ___HCRU RN ___ CCL ___

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Version 1.0 Date: 2/1/2018

Figure 4.16 Texas Children's Hospital cardiac catheterization laboratory safety checklist.

result on average in earlier discharge and return to normal daily functioning [34]. In pediatric surgery, ERAS efforts began later, but the few guidelines that do exist also seem to be efficacious in earlier recovery [35]. Pediatric cardiac surgery would seem to be an appropriate area to study this concept because of the complicated perioperative protocols in place, that have a number of common features despite a variety of cardiac lesions. Roy and colleagues reported on 155 patients eligible for a new Enhanced Recovery After Congenital Cardiac Surgery (ERACS) program [36]. Eligibility criteria included patients 1 month of age or older undergoing lower complexity surgeries, of STAT score (Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery Risk Category) 1–3, with few comorbid conditions that could affect recovery. Patients were identified preoperatively and listed as ERACS patients on the surgical scheduling system. Approaches and protocols were devised by a multidisciplinary group of stakeholders, including surgeons, anesthesiologists, intensivists, cardiologists, perfusionists, nurses, APPs, dieticians, respiratory care, child life, and rehabilitation medicine specialists. Education of perioperative caregivers in the approaches and protocol was undertaken. A graphic depiction of the major components is displayed in Figure 4.17. Adherence to the protocols was variable, ranging from perioperative nausea/vomiting prevention given in OR of 33%, multimodal analgesic regimen given in OR of 57%, ventilation <8 hours in 54%, to cell saver/tranexamic acid use in 97%; and multimodal pain regimen postoperatively in 100%. When compared to a historical matched control group of pre-ERACS patients, major indices such as mechanical ventilation >8 hours, ICU length of stay >1.25 days, and percent of patients with complications, and numbers of complications, were not different. This important initial effort emphasizes both the potential for improvement in ERACS indices if all guidelines were to be followed; but also the complexity and a high number of components to this approach. Further data will be required to understand its benefits, and if simplification and reduction in numbers of the parameters will promote better compliance with ERACS protocols.

TCH handbook

The TCH Heart Center has a number of educational and research conferences, mostly specific to the various disciplines, that will not be further detailed. One important recent multidisciplinary educational effort was the production of the Texas Children's Hospital Handbook of Congenital Heart Disease, created by a collaborative effort of authors from Surgery, Cardiology, Anesthesiology, ICU, Perfusion, Nursing, and other members of the Heart Center team [37]. The handbook is a series of short, informative, practical chapters about the approach to all of the major cardiac lesions at TCH, including the workup, surgical or catheter therapy, and ICU and postoperative care. The handbook has numerous echocardiogram, angiographic, and anatomical figures, and is designed to be a day-to-day source of information for all clinicians in the Heart Center, including trainees in all disciplines, APPs, and faculty level providers. The bedside nursing staff utilizes this resource frequently as well. The handbook is available in paper and electronic format for a nominal cost to the entire Heart Center, as well as to a wider

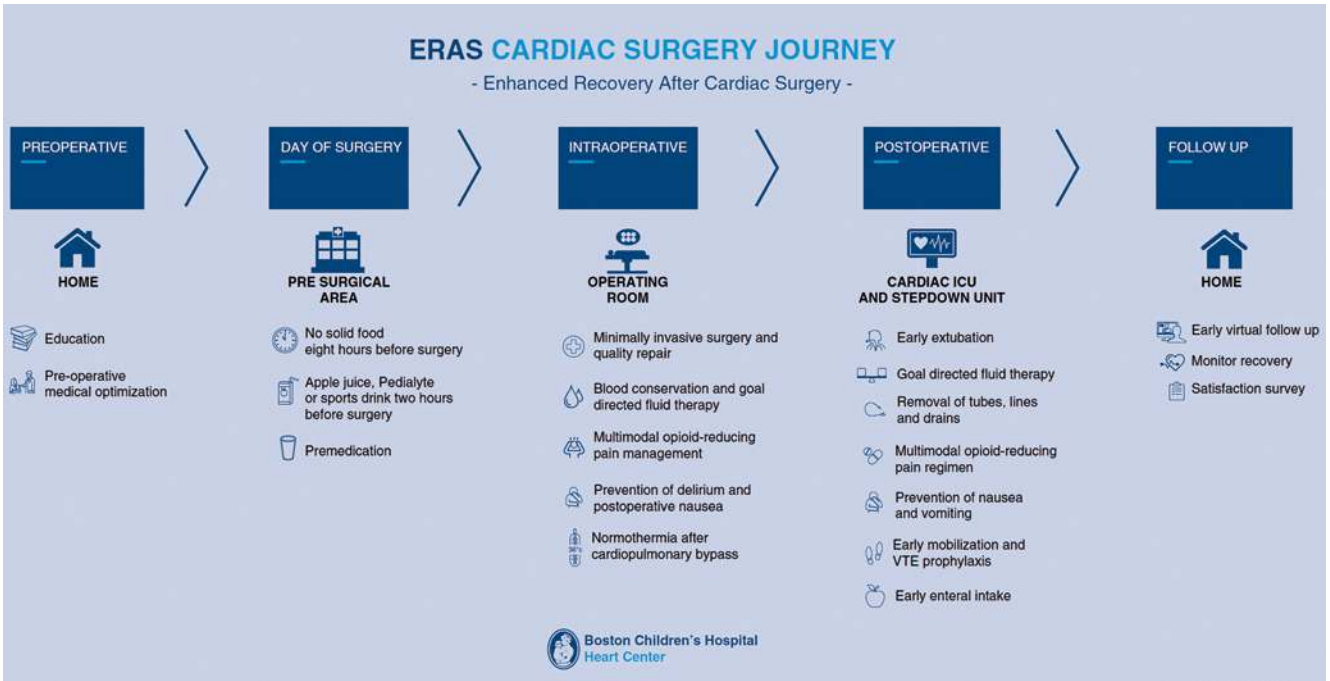


Figure 4.17 Major components of the Enhanced Recovery after Surgery Cardiac Program at Boston Children's Hospital throughout the patient's surgical journey. Evidence-based guidelines were developed for the program components, and targets were set by multidisciplinary stakeholders. ICU, intensive care unit; VTE, venous thromboembolism. (Source: Roy et al. [27]. Reproduced with permission from Elsevier.)

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audience through availability on major electronic platforms. An example from the handbook is displayed in Figure 4.18.

Parent and family involvement in congenital cardiac care

The multidisciplinary nature of congenital cardiac care also involves parents and family, and in the case of adult CHD often involves spouses and partners. This is a crucially important component of the overall care of the patient, and at the TCH Heart Center families are integrally involved in the care of their child; and invited to listen and contribute to patient care rounds in the ICU and wards, and ask questions of the caregiving team [38, 39]. The CICU is designed with sleeping and bathroom space for the family in the actual ICU room, and parents can be present 24 hours/day, with the exception of admission after procedures, or during certain emergencies. After discussion with parents, they are at times allowed to be present during invasive procedures and even resuscitation. Parental presence during induction of anesthesia for cardiac operations and catheterization procedures is not routinely offered but can be arranged in unique cases. Generous use of premedication, distraction with music, storytelling by child life specialists, and electronic devices, and allowing parents to be with the child until immediately before the transfer to the OR results in a smooth separation in almost all cases. Parents are informed of surgical progress every 1–2 hours, either in person by surgical APPs, or by a secure electronic communication system on their mobile phones. The surgeon meets with the family immediately after the surgery, and the parents are reunited with the child as soon as possible after ICU admission, usually within 60 minutes. After catheterization procedures, parents are allowed into the recovery area as soon as the handoff process to the nursing staff is complete. Parents of previous cardiac surgical patients were included in focus groups, and in the design committee for the Heart Center ICU and ward patient care areas.

Heart Center functioning during the COVID-19 pandemic

Prior to March 2020, the TCH Heart Center, as with most around the world, conducted conferences and meetings in

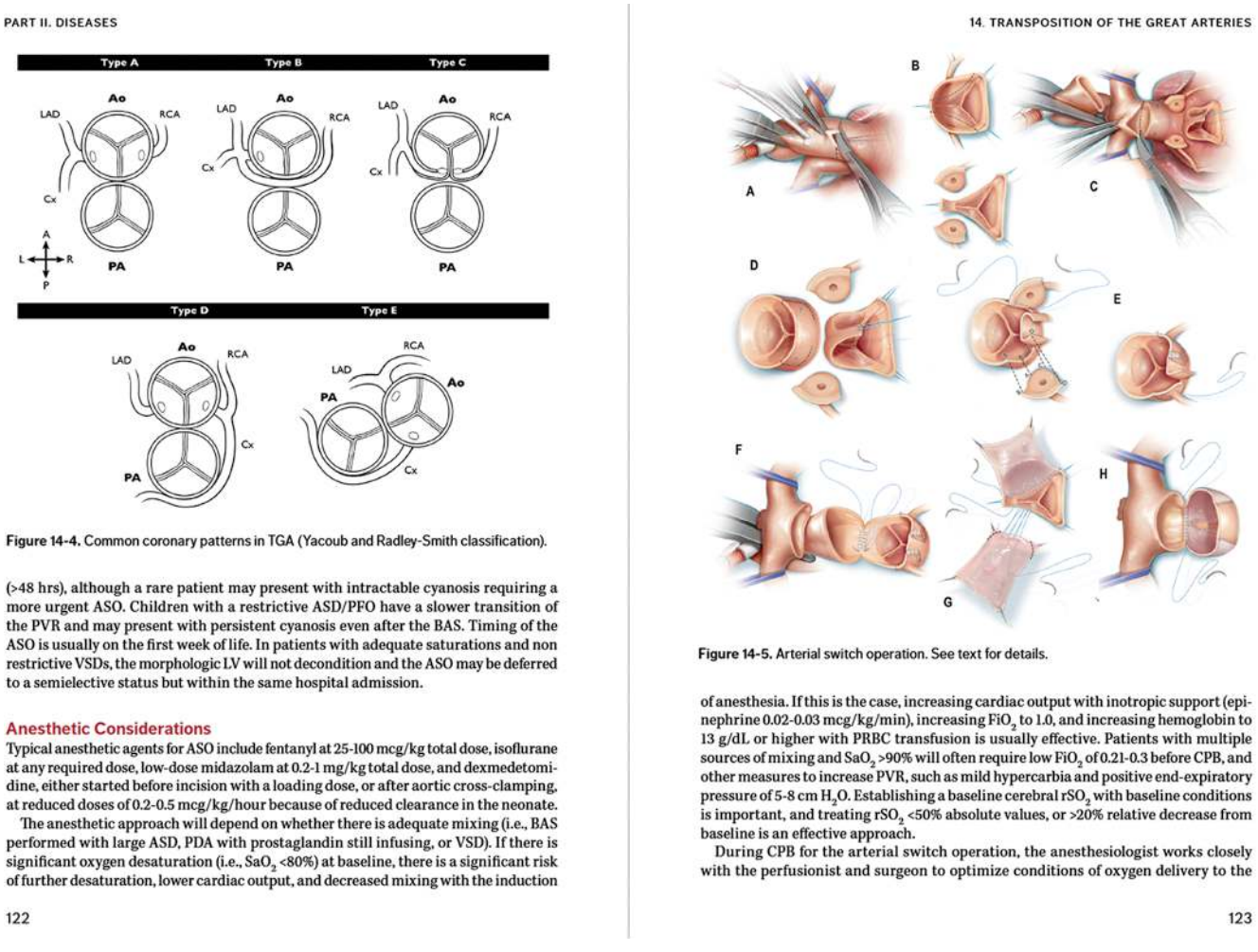


Figure 14-4. Common coronary patterns in TGA (Yacoub and Radley-Smith classification).

(>48 hrs), although a rare patient may present with intractable cyanosis requiring a more urgent ASO. Children with a restrictive ASD/PFO have a slower transition of the PVR and may present with persistent cyanosis even after the BAS. Timing of the ASO is usually on the first week of life. In patients with adequate saturations and non restrictive VSDs, the morphologic LV will not decondition and the ASO may be deferred to a semielective status but within the same hospital admission.

Anesthetic Considerations

Typical anesthetic agents for ASO include fentanyl at 25-100 mcg/kg total dose, isoflurane at any required dose, low-dose midazolam at 0.2-1 mg/kg total dose, and dexmedetomidine, either started before incision with a loading dose, or after aortic cross-clamping, at reduced doses of 0.2-0.5 mcg/kg/hour because of reduced clearance in the neonate.

The anesthetic approach will depend on whether there is adequate mixing (i.e., BAS performed with large ASD, PDA with prostaglandin still infusing, or VSD). If there is significant oxygen desaturation (i.e., SaO_2 <80%) at baseline, there is a significant risk of further desaturation, lower cardiac output, and decreased mixing with the induction

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Figure 14-5. Arterial switch operation. See text for details.

of anesthesia. If this is the case, increasing cardiac output with inotropic support (epinephrine 0.02-0.03 mcg/kg/min), increasing FiO_2 to 1.0, and increasing hemoglobin to 13 g/dL or higher with PRBC transfusion is usually effective. Patients with multiple sources of mixing and SaO_2 >90% will often require low FiO_2 of 0.21-0.3 before CPB, and other measures to increase PVR, such as mild hypercarbia and positive end-expiratory pressure of 5-8 cm H_2O. Establishing a baseline cerebral rSO_2 with baseline conditions is important, and treating rSO_2 <50% absolute values, or >20% relative decrease from baseline is an effective approach.

During CPB for the arterial switch operation, the anesthesiologist works closely with the perfusionist and surgeon to optimize conditions of oxygen delivery to the

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Figure 4.18 Two pages from the Texas Children's Hospital Handbook of Congenital Heart Disease, in the Transposition of the Great Arteries chapter. (Source: Mery et al. [37] / Reproduced with permission from Texas Children's Hospital.)

person, often with 100+ clinicians and others present and seated adjacent to one another in the main auditorium, and in the smaller but still crowded conference and meeting rooms for smaller groups for in-person meetings. Videoconferencing was occasionally offered to supplement the meetings, but the majority did not have this option. The COVID-19 pandemic forced a rapid change to all meetings converting to videoconferencing because of social distancing protocols, that persists at the time of writing this chapter. Although still encountering many of our colleagues from all disciplines during clinical care and individually in office areas, the camaraderie and opportunity for social exchange and networking within our own Heart Center, before and after the many conferences, has sadly been limited by the current arrangement. However, the excellent visibility of all the data displayed on one's office computer, and the ability to contribute opinions via the chat function in the videoconferencing system, have actually improved the quality of the conferences in these respects. The ability to join conferences from locations outside of the hospital has facilitated attendance and participation. Whether the TCH Heart Center will return to only in-person conferences in the future has not been decided, but some form of hybrid in-person/videoconferencing is likely.

Patient care has also been profoundly affected by the COVID-19 pandemic [40, 41]. Since April 2020, all patients coming for procedures requiring anesthesia have been tested within 72 hours of the procedure for SARS-CoV2 infection via polymerase chain reaction RNA testing and a number of elective procedures postponed because of symptomatic or asymptomatic infection; personal protective equipment protocols for aerosol-generating procedures were instituted and are still in place at the time of this writing [42, 43], and there have been several periods where Heart Center elective procedures have been limited because of high numbers of COVID-19 admissions and the need to care for some of these patients in the CICU because the Pediatric Intensive Care Unit (a separate unit at TCH) itself had no available beds [44]. A number of COVID-19 patients with cardiac involvement have also been a new category of medical admissions to the CICU [45–47]. Telemedicine, although limited in some CHD patients by the nature of their disease and the need to be seen in person, was initiated when appropriate and promises to change the way CHD patients are cared for after the COVID-19 pandemic [48]. Although numbers of surgeries and procedures for non-CHD areas of TCH decreased by as much as 20–30% during the height of the pandemic, CHD procedures in the operating rooms and catheterization laboratories decreased much less and only temporarily, again because of the nature of the diseases involved and the need for ongoing treatment. Finally, the longer-term sequelae of COVID-19 cardiac disease such as coronary artery aneurysms, and a decrease in myocardial function will be a concern for the Heart Center team in this new group of patients [49, 50].

Conclusions

In no field of medicine are multidisciplinary collaboration, team functioning, and communication more important than in CHD. The number, variety, and complexity of available therapies increase continually, as does the patient population served by institutions providing this care. In this chapter, we presented a Heart Center model that has grown and evolved as both provider and patient population have grown at TCH. Each institution will develop its own specific approach, but practicing the principles in this chapter should lead to increased communication and collaboration in a variety of settings. All caregivers in this ever-changing field owe this to the patients and families they serve, in order to maximize not just survival but the quality of life.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Daaboul DG, DiNardo JA, Nasr VG. Anesthesia for high-risk procedures in the catheterization laboratory. Paediatr Anaesth 2019; 29(5):491–8.
An excellent review of the highest risk procedures for the cardiac catheterization laboratory, with anesthetic considerations, and a recommended approach to multidisciplinary planning with the cardiac interventionalist and surgery teams.

8 Pype P, Mertens F, Helewaut F, Krystallidou D. Healthcare teams as complex adaptive systems: understanding team behaviour through team members' perception of interpersonal interaction. BMC Health Serv Res 2018;18(1):570.
A well written review of the theory of complex adaptive systems and the transformation from merely complicated to complex. The concept of complex adaptive systems in healthcare is being realized, where the focus is on interdisciplinary team members' interactions with each other, rather than the characteristics of individual team members, in their ability to adapt to the many changing conditions and challenges to the organization.

11 Duignan S, Ryan A, O'Keeffe D, et al.Prospective analysis of decision making during joint cardiology cardiothoracic conference in treatment of 107 consecutive children with congenital heart disease. Pediatr Cardiol 2018;39(7):1330–8.
A very interesting prospective evaluation of the approach of one congenital heart disease program's to presenting complex cases, and the inconsistency in some of its decision-making.

14 Hickey E, Pham-Hung E, Nosikova Y, et al.NASA model of "Threat and Error" in pediatric cardiac surgery: patterns of error chains. Ann Thorac Surg 2017;103(4):1300–7.
Presentation of a novel infographic approach to presenting the "flight" of congenital cardiac surgery patients, and assigning risk levels to their course, and determining whether threats and errors occur, and if they are responded to appropriately. In 12% of "flights" patients failed to de-escalate sequentially and in the timeframe expected through the risk levels. Failed de-escalations were strongly associated with errors (426 in 257 flights, $p<0.0001$). More serious errors were associated with a 29% rate of failed de-escalation, vs. 4% in flights with no consequential error ($p<0.0001$).

15 Torralba KD, Jose D, Byrne J.Psychological safety, the hidden curriculum, and ambiguity in medicine. Clin Rheumatol 2020;39(3):667–71.
A well written review of psychological safety in medicine, and how if it is lacking, patient care and outcomes can suffer, as well as education of the learners.

17 de Leval MR, Carthey J, Wright DJ, et al.Human factors and cardiac surgery: a multicenter study. J Thorac Cardiovasc Surg 2000;119(4 Pt 1): 661–72.
The landmark study of human factors, errors, near misses, communication, and rescue from negative events in multicenter study of 193 arterial switch operations. The number of uncompensated major events per case conferred the strongest risk of death at an odds ratio of 13 (95% CI 2.1–83, $p = 0.006$), and for each uncompensated major event, estimated odds of death increased by a factor of 5.7, and odds of death plus near miss were increased by a factor of 40.

20 Hardie JA, Oeppen RS, Shaw G, et al.You have control: aviation communication application for safety-critical times in surgery. Br J Oral Maxillofac Surg 2020;58(9):1073–7.
A very well written comparison of aviation safety with the operating room environment focusing on providing a multidisciplinary "sterile cockpit" during critical periods of an operation and during emergencies.

22 de Lind vanWijngaarden RAF, Siregar S, Legué J, et al.Developing a quality standard for verbal communication during CABG procedures. Semin Thorac Cardiovasc Surg 2019;31(3):383–91.
A video recording study of six coronary artery bypass graft (CABG) surgeries, and by personal interviews and focus group meetings with surgeons, anesthesiologists, and perfusionists, which arrived at 64 items deemed to be critical to communicate for safe CABG surgery. Substantive communication was present in 40% of exchanges, instubstantive communication in 33%, and no call back in 27%. This study demonstrated that optimal high quality communication could be improved, and provided an important patient safety standard for intra-team communication during CABG operations.

28 Mahle WT, Nicolson SC, Hollenbeck-Pringle D, et al.Utilizing a collaborative learning model to promote early extubation following infant heart surgery. Pediatr Crit Care Med 2016;17(10):939–47.
A multicenter study to increase the rate of early extubation for coarctation and tetralogy of Fallot repair. The rate of early extubation increased in the active sites from 11.7 to 66.9% ($p < 0.001$) with no change in reintubation rate. The median duration of postoperative ventilation among active sites decreased from 21.2 to 4.5 hours ($p < 0.001$).

37 Roy N, Parra MF, Brown ML, et al.Initial experience introducing an enhanced recovery program in congenital cardiac surgery (ERACS). J Thorac Cardiovasc Surg 2020;160(5):1313–21.
A single center multidisciplinary approach to protocolized care designed to shorten length of stay and complications. When compared to a historical matched control group of pre-ERACS patients, major indices such as mechanical ventilation >8 hours, ICU length of stay >1.25 days, and percent of patients with complications, and numbers of complications, were not different. This important initial effort emphasizes both the potential for improvement in ERACS indices if all guidelines were to be followed; but also the complexity and high number of components to this approach.

CHAPTER 5

Informatics and Artificial Intelligence in Congenital Heart Disease

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Introduction

The amount of patient data which can be leveraged for decision-making in critical care environments, such as operating rooms (ORs) and intensive care units (ICUs), continues to grow at an ever-increasing rate. While working in a data-rich environment has clear clinical benefits, the geometric growth of data generated per patient often leads to increasingly challenging situations for a single individual to manually review and assimilate all the data collected from a given patient with high fidelity. This is often referred to as the "data overload" problem. The field of informatics provides a structured framework for how to overcome this challenge. Applying the tools and technologies of informatics to the data, practices, and use cases inherent to anesthesia and critical care medicine yields powerful ways to enhance physician decision-making and improve patient care and safety. With the development of these tools, there is anticipated improvement in healthcare access, efficiency, quality, and outcomes.

This chapter will provide an overview of the history of medical informatics and emerging technologies. A brief examination of the basics of various data, data types, and common techniques in data mining will be discussed with a focus on their relative strengths and limitations. Finally, clinical examples of advanced analytics for congenital heart disease (CHD) and pediatric critical care medicine will be presented.

History of medical informatics

Biomedical informatics is a multidisciplinary field that studies the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem-solving, and decision-making to improve the medical care and health of patients [1]. The term "medical informatics" first appeared in the 1960s and undoubtedly has historical origin from the first computer, which was developed in 1945. The world's first electronic digital computer was developed at the University of Pennsylvania Moore School of Electrical Engineering. This computer was called the electronic numerical integrator and computer (ENIAC) and was utilized by the United States Army Ballistic Research Laboratory to study thermonuclear weapons and calculate artillery firing tables [2]. ENIAC played a role in the processing of Monte Carlo methods, which are a set of computational algorithms which rely on repeated random sampling to obtain numerical results [3]. The utilization of these methods and computational processing paved the way for applications in simulations, optimization problems, predictive modeling, probabilistic analyses, and applied statistics.

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Machine learning was first described in 1959 by Arthur Samuel in reference to a computer program which could iteratively improve each time it played a game of checkers [4]. What began with programs and algorithms for simple pattern classifications has now grown to a robust field with symbolic methods to analyze data. Over the next few decades, a crossover of computer technology into healthcare emerged. Computer technology began appearing in the 1970s at Veterans Affairs Hospitals and Massachusetts General Hospital [5, 6]. Meanwhile, database and database management continued to evolve from primitive file processing to database management systems from the 1970s to 1980s. This included hierarchical and relational database systems and query languages, such as structured query language (SQL) [7]. In the 1980s, the improvement of computer hardware technology and processing speeds led to improved capabilities to store and process data. With the improvement in the management of more complex data, further integration of heterogeneous data sources, development of advanced data models and queries, and sophisticated database management systems, the landscape of data storage and analysis evolved. By the late 1980s, the business data warehouse was developed by International Business Machines (IBM) researchers Barry Devlin and Paul Murphy [8]. The business data warehouse is a repository of multiple heterogeneous data sources, organized under a schema to facilitate business intelligence and decision-making. The applicability of data warehouses to medicine not only allowed for new techniques and fields to emerge but also created new problems to solve.

Meanwhile, a United States Defense Advanced Research Projects Agency (DARPA)-funded project led to computer networks and the Internet in the 1960s. This system of interconnected computer networks grew to the World Wide Web in the late 1980s and early 1990s [9]. Information retrieval, data mining, and web-based databases (XML or extensible markup language databases) soon became possible. Over the next few decades, the application of database and data warehouse technologies continued to expand from business to medical use.

With the adoption of the Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009, there was a large movement toward the meaningful use of health information technology and the standardization of electronic health records in efforts to improve medical care [10]. The patient data generated on a day-to-day basis in healthcare has led to major advancements in the field of medical informatics, particularly in the perioperative setting and ICU [11, 12]. Modern physiologic monitors can provide more than 20 continuous values at frequencies >200 Hz regarding a patient's status [13]. Similarly, the adoption of electronic health records, databases, and data warehouses has influenced medical informatics. The thoughtful design of these databases and communication standards is essential to ensure interoperability. Communication standards such as Health Level-7 (messaging), Digital Imaging and Communications in Medicine (imaging), and Institute of Electrical and Electronics Engineers/International Organization for Standardization 11 073 (device interoperability) have played a pivotal role in medical informatics [14]. Today, medical informatics is a field which intersects with clinical sciences, medicine, mathematics, computer programming, bioengineering, decision analysis, probability, epidemiology, and statistics.

KEY POINTS: HISTORY OF MEDICAL INFORMATICS

- Biomedical informatics is a multidisciplinary field that studies the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem-solving, and decision-making to improve the medical care and health of patients.
- The development and application of computer technology, databases, and data warehouses in healthcare have led to important advancements in electronic health records, data science, and data mining.

Principles, terminology, and technologies

This section provides an overview of medical informatics by describing basic principles, terminologies, and technologies. Its goal is to provide a framework to begin conceptualizing the use of data science in healthcare.

Friedman's fundamental theorem of informatics states that: "A person working in partnership with an information resource is 'better' than that same person unassisted" (Figure 5.1) [15]. The theorem describes how information technology is capable of augmenting human reasoning, and information resources may provide information, knowledge, or advice to support an individual who is faced with a medical decision. Friedman's fundamental theorem assumes that the resource offers something of benefit that the individual does not know. The interaction between the individual and information resource is critical.

For a technology to be truly useful, data is utilized to create information that the clinician utilizes and integrates with their knowledge. Through the repeated application of such knowledge, wisdom forms. The concept of knowledge

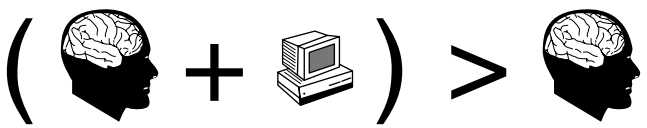


Figure 5.1 Friedman's fundamental theorem of informatics. (Source: Friedman [15]. Reproduced with permission of Oxford University Press.)

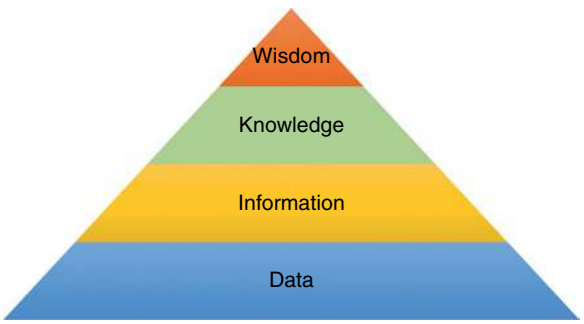


Figure 5.2 Data, information, knowledge, and wisdom hierarchy. Source: Adapted from Ackoff [16].

and wisdom creation from data has been adopted from Ackoff's data, information, knowledge, and wisdom hierarchy (Figure 5.2) [16–18].

- Data includes any number, text, symbol, image, and sound that may be stored and studied. Examples of data include vital signs (heart rate, respiratory rate, blood pressure, pulse oximetry), ventilator parameters, images, diagnoses codes, or free text in medical charts (Figure 5.3).
- Information processed data. An example of this is the interpretation of hypoxia based on pulse oximetry data.
- Knowledge is contextualized information where familiarity is gained by experience. In the perioperative environment, an example is an integration of information (hypoxia and high peak airway pressures) to utilize the knowledge and diagnose a mucous plug.
- Wisdom encompasses testable, consistently successful beliefs and involves the synthesis of knowledge to an elevated and shared understanding that is robust and repeatable. The safe perioperative care of patients with congenital heart disease requires vast knowledge, experience, and understanding of physiology to comfortably treat conditions such as hypoxia.

How to work with big data

Working with data is both an art and a science. Each data science project is unique in its goals and will therefore be unique in its design and execution. However, there are many best practices and frameworks that have been adopted by the data science community to ensure that high-quality and reliable results are achieved. To understand how to work with data, we must first understand how data is represented, measured, collected, organized, and accessed.

How is data represented

All data, from music to images to patient medical records, is ultimately stored as ones and zeros within a computer. These are referred to as bits. The bits are stored in the computer's volatile memory (random-access memory, RAM) or in non-volatile memory (i.e. files on a hard drive which are preserved across reboots of a computer). Typically, sets of 8 bits are grouped together. This grouping is called a byte. Data size is often measured in units of bytes, with ever-increasingly larger prefixes (Table 5.1). There are various systems to encode the data. Two examples include binary, which consists of two digits (0 and 1), or base-10, which consists of 10 digits (0 through 9).

To encode useful information, there are many ways to interpret patterns of bits. Different encoding types have different advantages and disadvantages. The most common data types for data science include the following.

Integers – This data type represents whole numbers (1, 2, 3, etc.). They can be signed or unsigned (i.e. positive or negative). The range of values that integers can have depends on the number of bits that are used to express their values. For example, an unsigned integer that uses 16 bits (or 2 bytes) can represent a number between 0 and 65 535 (2^16 – 1), while an unsigned 8-bit integer can represent a number between –128 and 127. Typical sizes for integers are

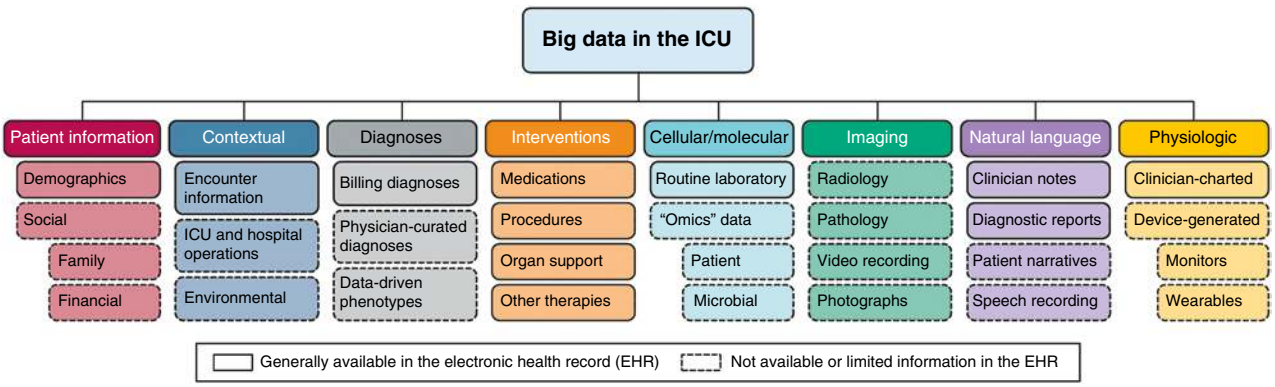


Figure 5.3 Sources of data in the intensive care unit (ICU) setting. (Source: Sanchez-Pinto et al. [21]. Reproduced with permission of Elsevier).

Table 5.1 Units of data

Units	Binary system	Base-10 system	Example
1 Bit (b)	Binary digit	Binary digit	'1' or '0'
1 Byte (B)	8 Bits	8 Bits	1 typed character (i.e. 'A')
1 Kilobyte (kB)	1024 Bytes	1000 Bytes	1 paragraph
1 Megabyte (MB)	1024 Kilobytes	1000 Kilobytes	400-page book
1 Gigabyte (GB)	1024 Megabytes	1000 Megabytes	30 minutes of video. 1 DVD movie is 4–8 GB)
1 Terabyte (TB)	1024 Gigabytes	1000 Gigabytes	500 hours of movies
1 Petabyte (PB)	1024 Terabytes	1000 Terabytes	500 billion pages of typed text or 2000 years of MP3-encoded music
1 Exabyte (EB)	1024 Petabytes	1000 Petabytes	11 million 4k resolution videos

Source: Gavin [19] and McKenna [20].

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8, 16, 32, and 64 bits. The disadvantage of integers is that they cannot express a number that contains a decimal or a fraction value.

Floating-point numbers – This data type represents positive and negative decimal numbers. The precision of floating-point numbers is based on the number of representative bits. They are usually represented as a decimal with an exponent (i.e. 2.3456×10^5). A 32-bit floating-point number has eight digits of precision (i.e. seven digits after the decimal), while a 64-bit float (usually called a double float) has 15 digits of precision.

Character arrays, strings, and text – This data type represents text. Usually, 1 or 2 bytes of data are used to represent an individual character, and character encoding maps are used to associate a specific byte value with a letter or pictograph (i.e. a character byte that has a value of 65 represents the letter "A"). The most common encoding maps are American Standard Code for Information Interchange (ASCII) and a universal character encoding standard called UNICODE. Traditionally, a string is terminated with a NULL character (i.e. the byte value of 0).

More complicated data representations are constructed hierarchically from these basic types. For example, a gray-scale image that has a resolution of 600×800 (such as that produced by an X-ray) can be represented using an array of 480 000 integers ($600 \times 800 = 480\,000$), where each integer represents the intensity of the signal at a specific location in the image. An RGB color image is represented using a set of three integers to represent a color for each pixel or location in the image. While there may be complex ways that these data structures are stored (because they can get very large), all complex data structures can be broken down into these fundamental data types for subsequent analysis.

Data types within a hospital

There are four main classes of data within a hospital: text-based records in the electronic medical system (EMR)/electronic health system (EHR), imaging data held in the Picture Archive and Communication System (PACS) system, physiologic time-series data generated by the bedside patient monitoring equipment, and genetic data from patients (-omics data). The most common data on medical data science projects include text-based records from the EMR. Within the EMR, there exists a further dichotomization of data: structured vs. unstructured data.

Structured data is data that has been captured in such a way that an unambiguous result can be ascertained from the user input. Conversely, unstructured data is data that is captured without such a rigorous process in place. For example, the entry of a patient's weight into the EMR using the "weight" field or ordering of a medication from a drop-down "medication list" are examples of creating structured data because there is a specific field on the form that was designed to capture "weight" and "medication name." It is not the nature of the data itself that is structured, but rather the *way* that the data is captured that determines if it is structured data. The limitation of a structured data capture system is that it can only capture data that it is designed to capture and nothing else. The benefit of a structured data capture system is that it facilitates data analyses and the data analysis pipeline (discussed later in this chapter).

Unstructured data is equivalent to the data generated while writing in the free-text portion of a clinical progress note. The free-text nature of unstructured data allows the user flexibility to add whatever information is important. The downside is that unstructured data is significantly more difficult to query than structured data. Imagine if a task is to obtain a list of the medication doses given to a set of patients. If these data were captured in a structured way, a spreadsheet could be generated with the medication name, corresponding dose, time, and patient (how this is done will be addressed later in this chapter). Unstructured data would require a manual chart review of all of the free text in the medical record to obtain the information. This process is time-consuming and may create errors that would potentially invalidate any data analysis. Often the most flexible systems have a mix of both structured and unstructured data. Significant forethought is given to the design of the structured fields to be captured and how the unstructured data will be utilized for analysis.

It is important to note that not all data that is generated in the hospital may be captured for retrospective review and analysis. Just because a piece of data is generated does not mean that it is stored. Oftentimes, there may be temporary storage of data that is purged in the future. A summary of the major data types and sources in an ICU setting is presented in Figure 5.3.

The lexicon of medical informatics and data science broadly encompasses terms related to various types of data, data analytics, and components of machine learning models (Table 5.2).

Table 5.2 Definitions and terminologies in medical informatics and data science

Term	Definition
Big data	Data generated in high volume, variety, and velocity, resulting in datasets that are too large for traditional data-processing systems.
Data science	A set of fundamental principles that support and guide principled extraction of information and knowledge from data.
Data mining	Extraction of knowledge from data via machine learning algorithms that incorporate data science principles.
Domain expertise	The understanding of real-world problems in a given domain (e.g. critical care medicine) that helps frame and contextualize the application of data science to solve problems.
Machine learning	The field of study that focuses on how computers learn from data and on the development of algorithms to make learning possible.
Features	The data elements (independent variables) used to train a model. Features may be raw data, transformations of raw data, or complex transformations of data (such as ones performed by neural networks).
Outcomes	The data elements (dependent variables) which represent the target for training in a supervised learning model. Outcomes may be categorical (e.g. yes/no)

(*Continued*)

Table 5.2 (Continued)

Term	Definition
	or continuous (e.g. length of hospital stay). Binary outcomes are typically represented as Boolean logic (e.g. true/false) or fuzzy logic (e.g. range of probabilities).
Supervised learning	Algorithms used to uncover relationships between a set of features and one or more known outcomes.
Unsupervised learning	Algorithms used to uncover patterns or groupings in data without targeting a specific outcome.
Model training	The process where machine learning algorithms develop a model of the data by learning the relationships between features. In supervised learning, the relationship between a set of features and one or more known outcomes is utilized for training. This is also referred to as model derivation or data fitting.
Model validation	The process of measuring how well a model fits new, independent data. For example, evaluating the performance of a supervised model at predicting an outcome in new data. This is also referred to as model testing.
Predictive model	A model trained to predict the likelihood of a condition, event, or response. The US Food and Drug Administration specifically considers predictive strategies as those geared toward identifying groups of patients more likely to respond to an intervention.
Prognostic model	A model trained to predict the likelihood of a condition-related endpoint or outcome such as mortality. In general, the goal is to estimate a prognosis given a set of baseline features, regardless of what ultimately leads to the outcome.
Overfitting	A phenomenon when an algorithm learns from idiosyncrasies in the training data, usually "noise." The noisy data present in the training dataset do not represent generalizable truth in relationships between features and outcomes. Overfitting will typically lead to poor model performance in an independent validation dataset.
Digitization	The conversion of analog data (e.g. paper documents, printed images) into a digital format (e.g. bits)
Digitalization	The wide adoption of digital technologies by an organization to leverage digitized data with the goal of improving operations and performance. The adoption of electronic health records, picture archiving, and pharmacy management systems are examples of digitalization in healthcare.
Data curation	The process of integrating data from different sources into a structured dataset. It typically involves authenticating data to ensure quality and may involve annotation of data to facilitate use in the analysis.
Structured data	Data (usually discrete or numeric) that are easy to search, summarize, sort, and quantify. Examples include vital signs and laboratory test results (e.g. complete blood count, complete metabolic panel).
Unstructured data	Data that do not conform to a prespecified structure. Unstructured data are usually more difficult to search, sort, and quantify. Examples include clinician notes, written narratives, images, pathology slides, radiology images, video, or audio.

Source: Sanchez-Pinto et al. [21]. Reproduced with permission of Elsevier.

Databases, data organization, and querying data

Structured data can be organized and recorded in databases to enable efficient storage and retrieval of information. While there are many types of databases, the two most common are relational databases and key-value storage systems (also called a NoSQL database or column stores). Relational databases allow a user to define relationships between sets of data so that data integrity and fidelity are rigorously and automatically enforced, while key-value databases provide ways of storing and retrieving large amounts of data without requiring the complexities and overhead associated with these guarantees. For the purposes of this discussion, we will focus on relational databases as these will be the most common databases utilized within the healthcare setting.

The structure of a relational database is called a schema, which is the organization or blueprint of the database. The schema is the database described by a set of one or more tables. A table is similar to a spreadsheet. Each table has its own set of rows and columns. The columns of a table (also called fields) represent the specific aspects of a set of data (i.e. "first name," "last name," and "date of birth"). Each field also has a type (such as integer, float, or text) to allow the database to understand how to interpret the data within each field. The rows of the table (also called records) represent the specific data points that have been recorded (i.e. "John," "Doe," "1-1-1970"). Each table must contain a column that has a unique identifier for each row. This is called the "primary key" field of the table. This is the equivalent of the row number in a spreadsheet. For most tables, this field is called the "record number" and is represented as a 64-bit integer, which allows for the unique identification of hundreds of millions of trillions of rows (or more precisely, 2^64 – 1 records).

The complexity of databases becomes evident when one considers the hundreds or even thousands of tables that need to be managed, linked, and organized. For example, a database associated with an EMR system may have more than 20 000 unique tables, and each table may have hundreds of fields. How is the subset of data located and retrieved in the haystack of tables defined in the database schema? The answer is through relationships. Generally, all tables in a database schema will be related to one another in some way, either directly or indirectly. A relationship between two tables is created by embedding the primary key of one table into a field within a different table. For example, imagine building a database to describe how beds are organized within a hospital ICU. Conceptually, hospital beds are organized into individual units, and each unit has one or more beds. The database schema can be represented using two tables: a "Units" table and a "Beds" table. Each table would have its own primary key and other fields related to the specifics of the table. The "Beds" table might have a field that is "bed name," while the "Units" table might have a field called "unit name." To create the relationship between the units and beds table, a field can be added to the beds' table, called unit ID, which can hold the record number of the record in the unit table that corresponds to the unit the bed is located. Therefore, to lookup what unit a given bed is located in, the following steps are executed:

1. Search the bed table to find the record associated with the name of the bed.
2. Extract the unit ID from the matching bed record.

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3. Search the units table to find the record with a primary key value equal to this unit ID.
4. Extract the unit name from the matching record.

Executing this process manually for dozens or hundreds of relationships between a large number of tables would be very tedious, but computers can be programmed to execute such searches as quickly and efficiently as possible. Computer scientists have created a structured language for querying database tables in order to efficiently search and extract data from databases. This language is called SQL (structured query language). SQL is a standard language that can be used to query data across a wide variety of databases such as MSSQL (Microsoft SQL), Oracle, and PostgreSQL among others. There are many textbooks and online tutorials available for learning how to write SQL queries that the reader can reference for further learning.

Data analysis and processing pipelines

Data processing pipelines are the processes by which heterogeneous data is collected and transformed into a standardized format for subsequent analysis (Figure 5.4). The data processing pipeline allows for the cleaning and integration of data. The process of creating knowledge from data includes the following steps:

1. **Data collection:** Data may be collected via a variety of methods that may include physiological sensors, monitors, or manual entry. This phase also involves data curation, which is the process of integrating data from different sources into a structured dataset. Depending on the size of the dataset, large amounts of data are often stored in databases or data warehouses. Database systems or database management systems are utilized to manage and access data. Data warehouses are a set of databases which hold information collected from multiple sources or locations.
2. **Data selection, feature extraction, and cleaning**: Relevant data is retrieved and may require transformation. Identification of relevant features, attributes, or dimensions of the data is imperative. Another essential process is the removal of noise and inconsistent data. There are techniques to filter, smooth, and estimate missing values by utilization of regression or outlier analyses. This stage also assesses the accuracy, consistency, completeness, interpretability, and believability of data. Occasionally, data integration (or the combination of multiple files, data sources, and databases) is necessary for the creation of a structured dataset.
3. **Analytical processing and algorithms**: Methods and algorithms are designed and then applied to extract data patterns. Descriptive tasks that characterize data can lead to a fundamental understanding of datasets. Predictive tasks can be performed on the dataset to make inferences on future patterns. In this process, elements of pattern evaluation can identify trends that may represent knowledge.
4. **Presentation and knowledge**: In this stage, data is visualized. Examples include data tables, bar charts, or pie charts. The processed data is represented as knowledge.

To ensure meaningful results, this process is often iterative and requires feedback from the data preprocessing or analytical processing steps. In addition, a strong understanding of the dataset via domain expertise is also imperative for meaningful inferences and insights.

KEY POINTS: PRINCIPLES, TERMINOLOGY, AND TECHNOLOGIES

- Friedman's fundamental theorem of informatics states that: "A person working in partnership with an information resource is 'better' than that same person unassisted."
- The data, information, knowledge, wisdom (DIKW) pyramid or hierarchy describes the relationship between data, information, knowledge, and wisdom.
- Common ways to encode data are with integers, floating-point numbers, character strings or text, and complex representations such as images. Various data types which can be studied include text-based records, imaging data, physiologic time-series data, and genetic data.
- Data science is a set of fundamental principles that support and guide principled extraction of information and knowledge from data.
- Relational databases allow for the efficient storage and retrieval of data through the structured query language.
- Data is converted to knowledge via processing pipelines that include data collection, data selection, feature extraction, data cleaning, analytical processing and algorithms, and presentation of knowledge.

Machine learning and artificial intelligence

Machine learning and artificial intelligence have grown from the fields of computer science, applied mathematics, and statistical learning. In general, machine learning is a field of

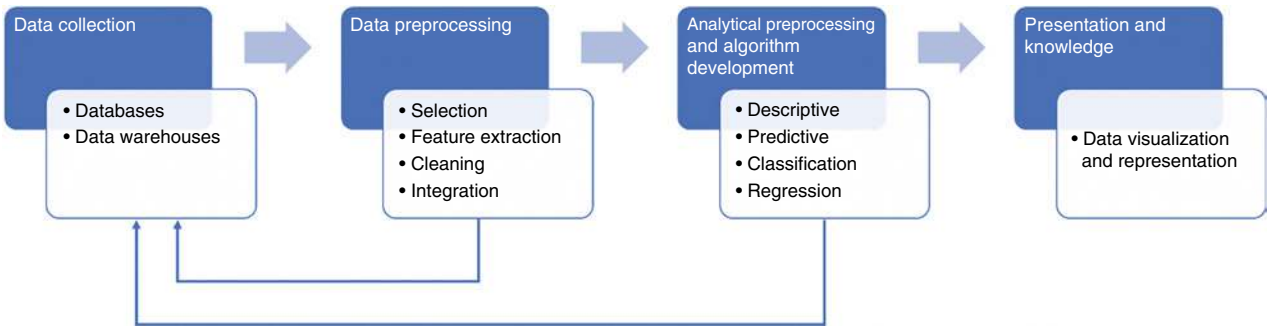


Figure 5.4 Data processing steps and pipeline.

study that focuses on the development of algorithms and methodologies for automating pattern recognition problems [22]. Humans are great at pattern recognition as our brains have had years of training to be able to recognize important aspects of our environment. Computers, on the other hand, have been traditionally poor at pattern recognition tasks.

A pattern recognition task is a task that requires a decision to be made by utilizing previous experiential knowledge of a regularized structure in sets of data. For example, suppose an individual is given a picture of either a cat or a dog and asked to determine which animal is displayed. Even though the exact picture of the cat or dog may not have been seen before, this task can be performed very accurately. Over time, the telltale features that make a cat a cat or a dog and dog have been learned. Using this set of learned, implicit features, the class of animal when a new dog or a cat is encountered may be inferred with a high degree of accuracy. Machine learning is a method for building algorithms that can learn the important "features" embedded within a large set of data and allow a computer to perform pattern recognition tasks automatically without human intervention.

In the field of genetics, molecular medicine, and bioinformatics, these algorithms have fostered discovery through advanced machine learning algorithms, biomedical ontologies, and natural language processing tools. As this field expands into the medical informatics domain, applications to clinical decision-making, methods for reasoning under uncertainty, knowledge representation, and systems integration are critical [23]. A large amount of available patient data has changed the way how we can approach clinical research and medical care [24, 25]. Machine learning is divided into three broad approaches: supervised learning algorithms, unsupervised learning algorithms, and broader, deep learning algorithms.

Supervised learning algorithms

Supervised learning algorithms are utilized to discover clinical features and relationships between variables of interest and outcomes [22]. Each data point is labeled or associated with a category or value of interest. Training data or examples are used to infer these relationships via learning algorithms. A research question addressed by a supervised learning algorithm may involve determining the clinical features that predict mortality in patients after congenital heart surgery (Figure 5.5A). The supervised learning algorithm is applied to a large training dataset to determine the relevant clinical features that predict the outcomes of interest. The goal is for these models to be applied to new patients to predict the pertinent outcome in a specific condition, event, or response.

Examples of supervised learning algorithms include linear regression, logistic regression, naïve Bayes, decision trees, and K-nearest neighbor. Once the algorithm is applied, the parameters of the model may then be adjusted and optimized on a subset/validation dataset. Once the learning algorithm is applied to the training dataset, performance is assessed via a testing dataset.

Unsupervised learning algorithms

Unsupervised learning algorithms are utilized to discover patterns or groupings in datasets without targeting a specific outcome [22]. The outcomes are unlabeled in unsupervised learning algorithms. These algorithms are often used in exploratory data analyses to find similarities in subsets of data. A research question addressed by an unsupervised learning algorithm may be used to determine groups of patients after congenital heart surgery and emerging patterns of clinical outcomes (Figure 5.5B). In this way, the dataset is automatically split into groups based on similarities. The goal of unsupervised learning algorithm is to organize the data to better describe features of the dataset structure.

Examples of unsupervised learning algorithms include hierarchical clustering, centroid-based/k-means clustering, principal component analysis, and latent class analysis. These algorithms are more computationally complex than supervised learning algorithms.

Deep learning algorithms

Deep learning algorithms or neural networks are a unique type of algorithm that consists of connected nodes or neurons, arranged in a series of layers to extract complex and meaningful features from data. Each node receives signal data, processes the data, and passes information to additional nodes. As learning proceeds in the neural network, the relative weights of each connection or edge are adjusted to strengthen the overall network [26]. A research question addressed by a deep learning algorithm may be utilized to extract meaningful diagnoses from patient chest radiographs (Figure 5.5C). The goal of deep learning algorithms is to solve complex medical problems with hierarchical complexity to make useful predictions.

Examples of deep learning algorithms include convolutional neural networks and generative adversarial networks. These algorithms require considerable computing resources and training sets. A summary of machine learning algorithms is presented in Table 5.3.

KEY POINTS: MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE

- Machine learning focuses on how computers learn from data and the development of algorithms and methodologies to make learning possible by leveraging the vast amounts of data available.
- Three broad categories of machine learning algorithms include supervised learning algorithms, unsupervised learning algorithms, and deep learning algorithms.
- Supervised learning algorithms are utilized to discover clinical features and relationships between variables of interest and outcomes. Models are developed through a training dataset and then validated through a testing dataset. Robust models can then be utilized to predict outcomes.
- Unsupervised learning algorithms are utilized to discover patterns or groupings in datasets without targeting a specific outcome. These algorithms are often used in exploratory data analyses to find similarities in subsets of data.
- Deep learning algorithms or neural networks are connected nodes or neurons, arranged in a series of layers to extract complex and meaningful features from data. These algorithms are utilized to solve complex medical problems with hierarchical complexity with the ultimate goal of making useful predictions.

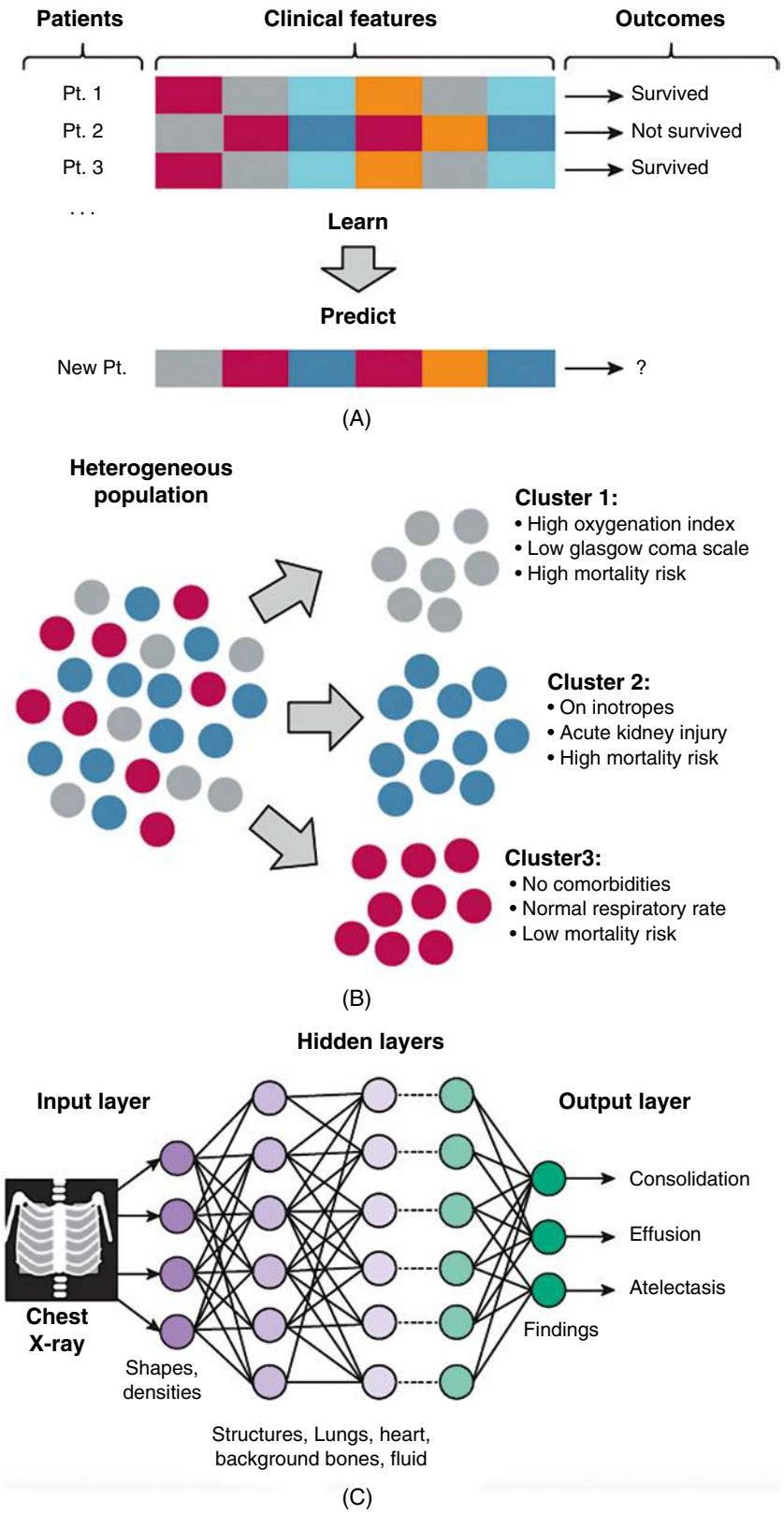


Figure 5.5 Types of machine learning algorithms: (A) supervised learning algorithms; (B) unsupervised learning algorithms; (C) deep learning algorithms. (Source: Sanchez-Pinto et al. [21]. Reproduced with permission of Elsevier).

Table 5.3 Examples of machine learning algorithms

Algorithm class	Examples	Description
Classic regression	Linear regression, logistic regression	Linear regression is a supervised learning algorithm that models the relationship between one or more features and a continuous outcome by fitting a regression line that minimizes the sum of all the residuals (distances between each feature in the training data and the line being fitted to model the data). Logistic regression is a generalization of the linear model that uses the logit function to estimate the probability of a binary outcome. To do this, the fitted sigmoid-shaped curve of the logistic function maps the feature values into a probability between 0 and 1.
Regularized regression	Lasso, ridge regression, elastic net	An extension of the classic regression algorithms in which a penalty is imposed to the fitted model to reduce its complexity and decrease the risk of overfitting.
Tree-based	Classification and regression trees, random forest, gradient boosted trees	A class of supervised learning algorithms based on decision trees. Decision trees are a sequence of "if-then-else" divisions that are derived by iteratively separating data into groups based on the relationship of the features with the outcome. Random forest and gradient boosted trees are examples of ensemble tree models. Ensemble models combine the output of many trained models to estimate an outcome.
Support vector machines	Linear, polynomial, radial basis kernel	A class of supervised learning algorithms that represents the data in a multidimensional feature space and then fits a "hyperplane" that best separates the data on the outcomes of interest. A hyperplane is a space with one dimension less than its space. For example, an n-dimensional space, a hyperplane that separates the space has (n – 1) dimensions.
K-nearest neighbor	K-nearest neighbor	A type of supervised learning algorithm that represents data in a multidimensional feature space and uses local information about observations closest to a new example to predict the outcome for that example.
Bayesian	Naïve Bayes, Bayesian network	A class of supervised learning algorithms that use Bayes' theorem of conditional probability, which is the probability that something will happen given that something else has already occurred. In general, Bayesian algorithms work by iteratively updating the probability of an outcome given new data.
Neural network	Artificial neural network, deep neural network	A class of nonlinear algorithms built using layers of nodes that extract features from the data and perform combinations that best represent the underlying structure, usually to predict an outcome. Neural networks can be shallow (e.g. perceptron with two layers) or deep (multiple layers), which form the basis for the field of deep learning.
Dimensionality reduction algorithms	Principal component analysis, linear discriminant analysis	A class of unsupervised learning algorithms that exploit the inherent structure in the data to describe data using less information. Principal components, for example, summarize a large set of correlated features into a smaller number of representative features.
Latent class analysis	Latent class analysis	A type of unsupervised learning algorithm that identifies unseen subgroups or latent classes, in the data. Class membership is unknown for each example, so the probability of class membership is indirectly estimated by measuring the patterns in the data.
Cluster analysis	K-means, hierarchical cluster analysis	A class of unsupervised learning algorithms that uses the inherent structures in the data to best organize the data into subgroups of maximum commonality based on a distance measure between features.

Source: Sanchez-Pinto et al. [21]. Reproduced with permission of Elsevier.

Advanced monitors in intensive care units and operating rooms

With advancements in medical informatics, computational processors, ICU monitors, and methods of information storage, we have entered an era of data-driven healthcare. The data analytics, algorithms, and methods described earlier in this chapter can be used in the development of new paradigms for the monitoring and treatment of patients with congenital heart disease. At present, monitoring systems are limited in scope for the prediction of adverse events, the opportunity of the development of intelligent monitoring systems is real.

Historical and real-time physiologic patient data can now be synthesized to create an integrated representation of the patient's overall state of health. For example, physiological trend graphs have been used to identify late-onset sepsis in preterm infants with increased accuracy in neonatal ICUs [27]. In future ICU monitors, relevant medical information, including patient-specific alarm conditions, risk-index scores, and suggestions for care, may be displayed in a unified monitor. There is a substantial benefit in the creation of displays that not only integrate the sizable amount of ICU data in a meaningful way but also provide the medical team with a display that allows a patient's clinical trajectory to be followed over time.

In addition to physiologic patient monitors, medical devices in the ICU and OR environments also have interfaces capable of submitting data that can be analyzed, i.e. infusion pumps, ventilators, extracorporeal membrane oxy-

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genation (ECMO) machines, ventricular assist devices, dialysis machines, etc. In addition, EMR data, i.e. problem lists, prior procedures, chronic medications, allergies, etc., can be integrated into the predictive models for a more robust dataset [28, 29]. Besides predicting risk for adverse outcomes, models could be designed to predict readiness to wean from support, i.e. inotropic, mechanical, ventilatory, or renal support [30].

Current pediatric risk and acuity scores include the Pediatric Risk of Mortality, the third version of PRISM (PRISM III) and Pediatric Index of Mortality, second version (PIM II). These scores take discrete physiological values at a moment in time to calculate a risk for mortality and ICU length of stay [31–34]. Consequently, they are limited for real-time analysis compared to high-resolution, physiologic data, which may allow for the development of metrics that may be more specific and sensitive in defining a patient's acute or impending acute condition.

Statistical or machine learning algorithms, such as classification trees, logistic regression, random forest algorithms, neural networks, or probabilistic network models have been utilized to create sophisticated models of disease [35, 36]. Data from the publicly available Physionet database has been utilized in artificial neural networks to create models for the detection of adult ICU patients at high risk of clinical deterioration with improved performance than traditional acuity scores [37, 38]. Neural networks have also been utilized to diagnose arrhythmogenic cardiac arrest, tension pneumothorax, pericardial tamponade, venous air embolism, and exsanguination [39]. In a multicenter study using electronic health record information, Churpek and colleagues have utilized machine learning methods to predict cardiac arrest, ICU transfers, and mortality in an adult hospital ward in a dataset of >250 000 hospital admissions [40].

The pursuit of such real-time analytics and risk prediction is an evolving field. Most modern medical decision support systems, often Internet or software based, utilize an advanced display to allow clinicians to visualize solutions to medical problems [41]. At the University of Michigan, complex network infrastructures capture and link physiologic data from patient monitors, electronic health record data, and anesthesia records to SQL databases, which are then utilized to create patient risk scores and more intelligent alarms in the ICU and OR settings [42] (Figure 5.6). The system was designed to classify patient physiologic states (such as hypotension), generate alerts, and provide notifications to clinicians.

In the CHD population, single ventricle patients have a high risk of interstage mortality and cardiac arrest. Mortality rates have been observed to be 12% described in the Single Ventricle Reconstruction Trial [43]. Additional analyses of the Single Ventricle Reconstruction Trial data have identified mortality rates or need for cardiac transplantation at 12 months to be 36% for patients receiving a modified Blalock-Taussig shunt and 26% for the right ventricle-to-pulmonary artery shunt. Most commonly, mortality was attributed to cardiovascular causes [44]. Rusin and colleagues have utilized continuous, high-resolution, physiologic recordings to develop logistic regression models that predict cardiopulmonary deterioration 1–2 hours prior to the event with a model area under the receiver-operating characteristic curve of 0.91–0.96 [45–47] (Figure 5.7). Ruiz et al. utilized naïve Bayesian models for the prediction of critical events 1–8 hours prior to the event with the area

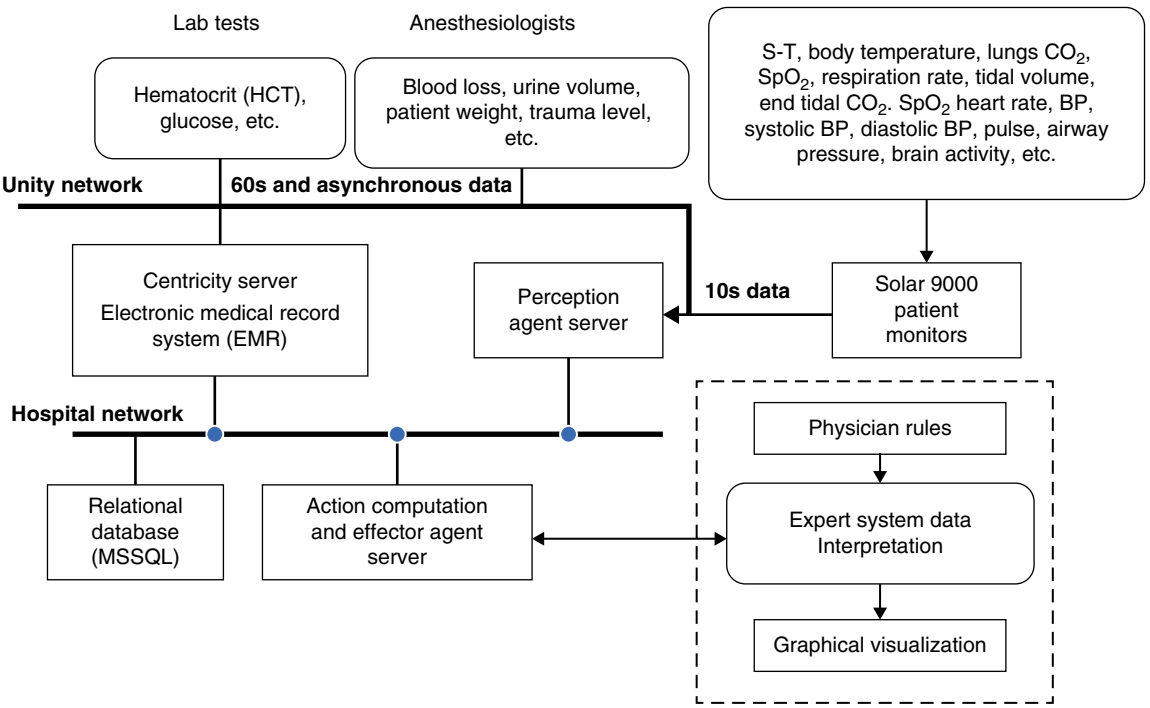


Figure 5.6 Example network architecture and data flow diagram for a clinical decision support system. BP, blood pressure; MSSQL, Microsoft Structured Query Language. (Source: Kruger [42] / The Open Cybernetics & Systemics Journal / CC BY-SA 4.0).

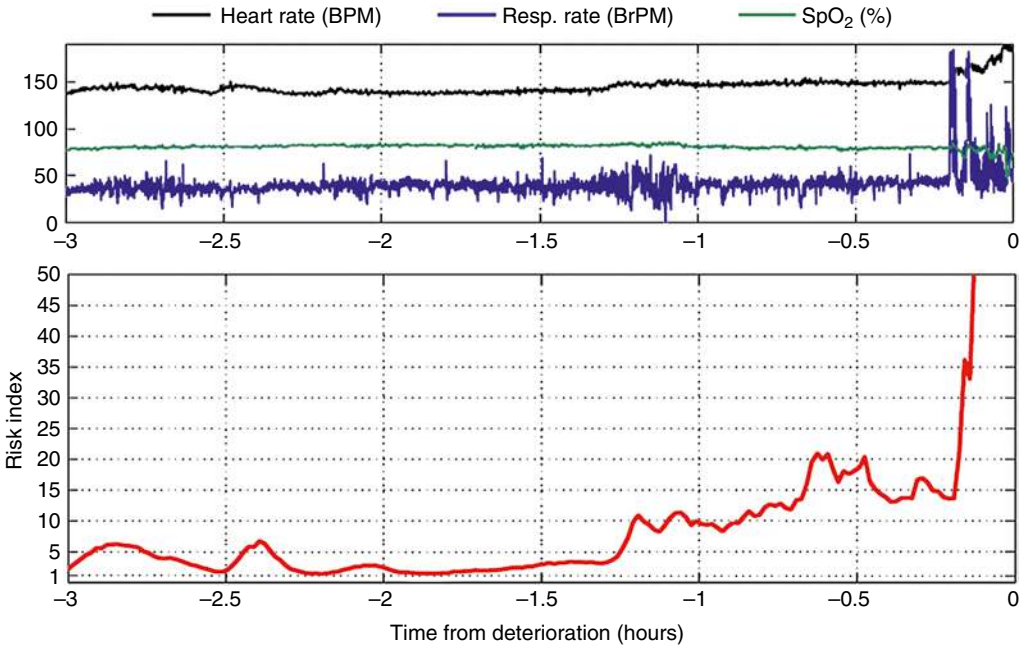


Figure 5.7 Real-time risk index for cardiopulmonary deterioration based on vital sign monitoring. Classification algorithms were applied and optimized to create receiver operating characteristic curves of 0.91. (Source: Rusin [45]. Reproduced with permission of Elsevier).

under the receiver-operating characteristic curves ranging from 0.73 to 0.88 [48]. These results are encouraging and suggest that computational models are able to detect subtle physiological changes in high-risk interstage patients and provide a real-time risk assessment for clinical deterioration. The results of these models are to be tested and validated via further multicenter studies. Early recognition of impending deterioration allows the medical team time for interventions in hopes of reducing patient morbidity and mortality.

The future of monitoring congenital heart disease will continue beyond the OR and ICU environment. In single ventricle patients, home monitoring and telemedicine systems have been proposed to improve outcomes [49–52]. Surveillance through tablet or personal computer-based solutions has been developed to facilitate communication between families and clinicians [53]. However, there are opportunities for growth and improvement as these home monitoring programs consist of basic vital sign monitoring. The expected future growth and expansion of home monitoring technologies and techniques beyond the hospital setting may continue to improve patient outcomes in the high-risk single ventricle patient.

KEY POINTS: ADVANCED MONITORS IN INTENSIVE CARE UNITS AND OPERATING ROOMS

- The data analytics, algorithms, and methods described earlier in this chapter can be used in the development of new paradigms for the monitoring and treatment of patients with congenital heart disease.
- Previous risk index and acuity scores include the Pediatric Risk of Mortality, third version (PRISM III), and Pediatric Index of Mortality, second version (PIM II) that use discrete values to predict mortality risk and ICU length of stay.
- Real-time analytics and risk prediction is an evolving field utilizing advanced data analytics. Logistic regression and naïve Bayes models have been utilized in single ventricle patients in the prediction of critical events such as cardiopulmonary arrest.

Limitations and challenges

With the development of new technologies from the field of medical informatics, there are limitations and challenges not only in the development of the technology but also in the adoption of that new technology. This section will discuss some of the pitfalls with the development of this technology and data mining.

Many advances have been made in medical informatics in the digitalization and integration of medical devices. However, poor integration and interoperability between medical devices remain a challenge for the data scientist when attempting to contextualize vast amounts of data. As the field of medical informatics has grown, the development of domain expertise, which must bridge the areas of computer science, statistics, engineering, and medicine, becomes even more important over the next decades. An understanding of both the data science and clinical applicability is needed to avoid the failures that commonly face new medical technologies. Otherwise, data mining may lead to irrelevant, flawed, or low-quality research [54, 55]. For

example, an issue described earlier in this chapter includes the overfitting of models. A rigorous approach to statistical and data mining methods through validation and testing can be utilized to detect this problem.

The US medical system is burdened with 180 000–440 000 preventable medical errors leading to patient mortality on an annual basis [56, 57]. There are constant pursuits to use the techniques described in this chapter to design advanced monitors for earlier and more reliable detection of adverse patient events. However, the burden of alarm fatigue to the user is a significant challenge in the critical care, OR, and perioperative care settings. In a pediatric ICU study, it was found that 68% of alarms were false and 94% of alarms were clinically unimportant [58]. A national survey among Canadian anesthesiologists found that 58% of 789 respondents routinely deactivated alarms at the start of a case [59]. Simple, rule-based decision support systems have been described for congestive heart failure. However, when the performance of the clinical decision support system was evaluated against manual review of records, the tool had a sensitivity of 79% and a positive predictive value of only 11% [60]. The system failed and was removed from clinical use, but it was able to highlight problems with false negatives, excessive alerts, and lack of physician response to alerts. In the design of clinical decision support systems, alarm management will play an essential role.

The widespread adoption of electronic health records and data warehouses has increased the accessibility of patient information. Information overload is an emerging concern, and the data from multiple devices that the medical provider can process, code, and integrate is finite [13, 61]. An important principle in the design of advanced monitors and clinical decision support tools is in the visual presentation of the information, which must be intuitive to the provider, who may not be familiar with the theory or evidence. The use of human factors science in the design of clinical decision support tools is pivotal to the success of new monitors.

The Gartner Hype Cycle describes a common pattern that arises with new technologies and innovations (Figure 5.8). The innovation trigger begins with a breakthrough and product launch. This is followed by a peak of inflated expectations where the expectations may be greater than the technological capabilities. A trough of disillusionment follows as problems with the technology lead to reduced expectations and slow adoption. Continued work and understanding of technology lead to a slope of enlightenment, and finally, a plateau of productivity forms where the technology finally finds productive and useful value [62]. The Gartner Hype Cycle highlights the challenge in the adoption of new technologies as perceptions and expectations of that technology must align with reality. In this way, the technology finally begins to impact patient care.

KEY POINTS: LIMITATIONS AND CHALLENGES

As medical informatics, machine learning, and artificial intelligence continue to grow in the perioperative and critical care settings, there are challenges in domain expertise, appropriate application of algorithms, model overfitting, and adoption of new technologies.

Future of clinical informatics in congenital heart disease

Though many clinical informatics systems in congenital heart disease are still in early stages of development, they will continue to evolve. As patient data, databases, and data warehouses continue to grow in scope and size, so will the medical system's contextual knowledge base and ability to develop models through advanced computational techniques. Data-driven systems will be transformative in guiding care for complex patient with congenital heart disease.

There have been several developments that have made the growth of medical informatics possible: (i) the increased collection and digitalization of data in medicine, (ii) the extraordinary expansion of computational power, (iii) the growth of the data science movement and its expansion into medical space, and (iv) the increasing availability of educational resources and tools for data science. These tools are a natural

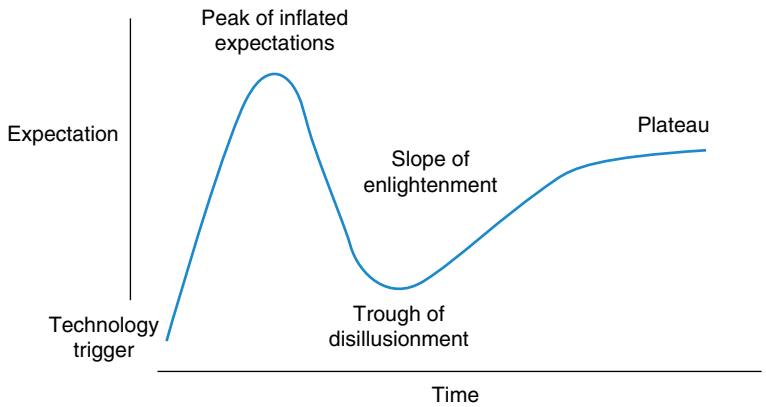


Figure 5.8 Technology Hype Cycle. (Source: Adapted from Gartner Hype Cycle for Artificial Intelligence, 2019 gartner.com/smarterwithgartner).

evolution in information technology, and as they continue to grow, so will the next-generation monitors that can provide the medical team with more effective tools for the early recognition of patient conditions to facilitate improved patient care.

This chapter has been designed to provide an overview of data science and machine learning techniques used in the development of future monitors and clinical decision support systems. We encourage further study in this complex field in those interested. Teams of engineers, computer scientists, data scientists, and clinical experts are required as the fields of clinical informatics, machine learning, and artificial intelligence expand in the perioperative setting. As the collection of data continues to grow, the data scientist and clinician can begin to embrace the complexities of congenital heart disease, critical care medicine, and emerging computational technologies [63, 64]. In the future, the multidisciplinary team will be responsible for the design of technologies for intelligent, safe, and effective patient care in patients with congenital heart disease.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

1 Kulikowski CA, Shortliffe EH, Currie LM, et al. AMIA Board white paper: definition of biomedical informatics and specification of core competencies for graduate education in the discipline. J Am Med Inform Assoc 2012;19(6):931–8.
The American Medical Informatics Association defines the field of biomedical informatics, its scope of practice, competencies, theory, methodology, and technical approaches.

21 Sanchez-Pinto LN, Luo Y, Churpek MM. Big data and data science in critical care. Chest 2018;154(5):1239–48.
An overview of various types of Big Data and methods of Data Mining in critical care environments.

22 Deo RC. Machine learning in medicine. Circulation 2015;132(20):1920–30.
An overview of machine learning techniques in medicine and illustrative clinical examples of supervised and unsupervised machine learning techniques.

40 Churpek MM, Yuen TC, Winslow C,et al. Multicenter comparison of machine learning methods and conventional regression for predicting clinical deterioration on the wards. Crit Care Med. 2016;44(2):368–74.
An observational, multicenter, cohort study examining accuracy of machine learning techniques for detecting clinical deterioration in the adult medicine ward. The random forest model was the most accurate model with an area under the receiver operating characteristic curve of 0.80.

42 Kruger G, Chen C, Blum J, Shih A, et al. Reactive software agent anesthesia decision support system. J Syst Cybern Inf 2011;9:30–7.
Application of complex network infrastructures to capture and link physiologic data from anesthesia patient monitors, electronic health record data, anesthesia records, and Structured Query Language databases.

43 Ghanayem NS, Allen KR, Tabbutt S, et al. Interstage mortality after the Norwood procedure: results of the multicenter single ventricle reconstruction trial. J Thorac Cardiovasc Surg 2012;144(4):896–906.
A review of mortality outcomes from the Single Ventricle Reconstruction Trial, the multicenter study randomizing subjects with single morphologic right ventricles to receive modified Blalock-Taussig shunt or right ventricle-to-pulmonary artery shunts. Overall interstage mortality is 12%.

46 Vu EL, Rusin CG, Penny DJ, et al. A novel electrocardiogram algorithm utilizing ST-segment instability for detection of cardiopulmonary arrest in single ventricle physiology: a retrospective study. Pediatr Crit Care Med 2017;18(1):44–53.
Signal processing of the electrocardiogram signal, quantifying ST-segment instability is a metric associated with cardiopulmonary arrest in single ventricle physiology.

47 Rusin CG, Acosta SI, Vu EL, et al. Automated prediction of cardiorespiratory deterioration in patients with single ventricle. J Am Coll Cardiol 2021;77(25):3184–92.
A real-time computer algorithm utilizing a logistic regression model was developed and validated to automatically recognize physiological precursors of cardiopulmonary deterioration in children with single ventricle physiology during the interstage hospitalization. The algorithm is able to provide 1–2 hours of advanced warning for 62% of all cardiorespiratory deterioration events with an area under the receiver operating characteristic curve of 0.958.

48 Ruiz VM, Saenz L, Lopez-Magallon A, et al. Early prediction of critical events for infants with single-ventricle physiology in critical care using routinely collected data. J Thorac Cardiovasc Surg 2019;158(1):234–243.e3.
Naïve Bayesian models were utilized to create predictive models for cardiopulmonary resuscitation, emergent intubation, or extracorporeal membrane oxygenation in single ventricle patients in the interstage hospitalization. Models predict critical events 1–8 hours prior to the event with an area under the receiver-operating characteristic curve ranging from 0.73 to 0.88.

49 Ghanayem NS, Hoffman GM, Mussatto KA, et al. Home surveillance program prevents interstage mortality after the Norwood procedure. J Thorac Cardiovasc Surg 2003;126(5):1367–77.
Institution of home surveillance programs, consisting of daily weight and pulse oximeter measurements, improves interstage survival after Norwood procedure.

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CHAPTER 6
Development of the Cardiovascular System

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Introduction

Congenital heart disease (CHD) is the most common birth defect, occurring in 0.8% of live births and accounting for almost one-third of all major congenital anomalies [1, 2]. The etiology and mechanisms of congenital cardiac malformations are not yet fully understood, and much of our understanding is derived from vertebrate animal models and progress in genomics, proteomics, transgenesis, imaging, and integrative systems biology [3]. CHD is known to have genetic and non-genetic causes, and the multifactorial inheritance of some lesions is probably due to the interactions between several genes, transcriptional programs, and modulating environmental factors, including known teratogens (such as alcohol, isotretinoin, excess vitamin A, thalidomide, anticonvulsants), infectious agents (such as rubella), or maternal diseases (such as diabetes mellitus, obesity, phenylketonuria) [4, 5]. Developmental mechanisms include genetic (somatic or germline variants, chromosomal aneuploidy, copy number variants, point mutations), epigenetic (transcriptional programs, chromatin remodeling factors, histone-modifying proteins), and hemodynamic and contractile forces [4, 6–10]. Furthermore, the understanding of genes and developmental mechanisms producing CHD has provided an insight into adult cell lineages and has opened the door for using regenerative medicine and novel therapies to treat congenital and acquired heart diseases [11]. It must be stated that much of the knowledge and understanding we have regarding cardiovascular development was derived from research in non-human species, which was performed with the hope that the same processes occur in humans.

We have used an anatomical approach to describe the development of the heart and vascular system and to demonstrate the relationships between abnormal development and specific congenital cardiac anomalies. Although a segmental approach is used to describe embryology, cardiovascular development is a three-dimensional, spatiotemporal process with many elements occurring simultaneously.

Contemporary concepts of cardiac development

Up until the 1990s, the conventional view of cardiac development was based on the *segmental model*, in which the primordia of all the future components of the heart were hypothesized to be present in the initial heart tube [12]. Many of the classic concepts have been challenged over the last two decades as advancements have been made in labeling and transgenic fate-mapping techniques. Although the labeling studies performed by Stalsberg, de la Cruz, and Viragh from 1969 onward suggested that cells were added to the poles of the heart from the surrounding mesoderm [13–15], more recent research conducted by Buckingham, Markwald, and others have

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confirmed that cells are added to the heart after the initial stage of looping [16–19]. As discussed in detail in the following sections, it is now thought that the primitive heart tube contains little more than the precursors for the left ventricle, parts of the atria, and perhaps the atrioventricular (AV) canal, and that the precursor cells of the other cardiac components are added to both the venous and arterial poles from a second heart field outside the initial heart tube [12, 20]. As stated by Christoffels and Jensen, cardiac development is an iterative process of progenitor cell expansion, intercellular signaling, transcriptional responses, patterning, and differentiation into specialized cell types [20]. Elucidation of the genetic and transcriptional networks regulating cardiac development has provided new insights in that abnormal development not only results in CHD but also influences adult-onset heart disease such as cardiomyopathies, conduction defects, and arrhythmias [21].

Cardiovascular development: normal and abnormal

The human embryo has no heart or vascular system during the first 2 weeks of life. Instead, it relies on diffusion from the uteroplacental circulation. At the end of the second week, the embryo is a bilaminar disc made up of the epiblast and the hypoblast. In vertebrates, the cardiovascular system is the first organ system to develop and function; this begins during the third week of life when diffusion is no longer adequate to meet embryonic nutritional requirements and to remove metabolic waste. The embryo develops into a trilaminar disc by the process of gastrulation, thereby establishing all three germ layers – the ectoderm, mesoderm, and endoderm. Gastrulation involves cells in the epiblast migrating through the primitive streak caudal to the primitive node. These cells detach from the epiblast (invagination), and some displace the hypoblast to create the embryonic endoderm, others come to lie between the epiblast and endoderm to form the mesoderm, and the remaining epiblast cells form the ectoderm (Figure 6.1) [22]. The epiblast is therefore the source of the ectoderm, mesoderm, and endoderm.

Cardiogenic fields

Cardiac progenitor cells are located in the epiblast just lateral to the primitive streak. After gastrulation, these progenitor cells in the lateral plate mesoderm migrate laterally and cranially to locate on either side of the midline under the head folds. The lateral plate mesoderm becomes split by the pericardial coelom into the somatic (dorsal) and splanchnic (ventral) layers (Figure 6.2). Cells in the somatic layer will form the pericardium and cardiac progenitor cells located in the splanchnic layer will form the bilateral cardiogenic or heart fields [24]. These cardiac progenitor fields express the transcription factor *NKX2.5* throughout the left ventricle and atrial chambers, a member of the Homeobox-containing genes that play critical roles in regulating tissue-specific gene expression essential for tissue differentiation and for temporal and spatial patterns of development [25]. The heart fields merge in the midline, cranial to the stomatopharyngeal membrane, to form the *cardiac crescent* (Figure 6.3A,B). There are at least two distinct lineages of cells within the cardiac crescent: one population is referred to as the "first heart field" (FHF), and the other is referred to as the "second heart field" (SHF) [10]. The SHF is contiguous with and located dorsal and medial to the FHF. The FHF will give rise to the linear heart tube and eventually gives rise to the left ventricle (LV) and parts of the right and left atria [27]. Cells from the SHF will be added at the inflow (venous) and outflow (arterial) poles during cardiac looping, ultimately giving rise to the right ventricle (RV), parts of the atria, septum and outflow tract, and base of the aorta and pulmonary trunk. Cardiac cell lineage and specification are shown in Figure 6.4 [27]. Differentiation of the heart field cells into the myocardium is dependent on signals from the neural and dermal ectoderm and adjacent endoderm [28]. The proliferation and differentiation of SHF cells are delayed relative to those of the FHF cells. As discussed in the following sections, the embryonic cells that contribute to cardiac development arise not only from the heart field mesoderm but also from the cardiac neural crest [29] and the proepicardium [30].

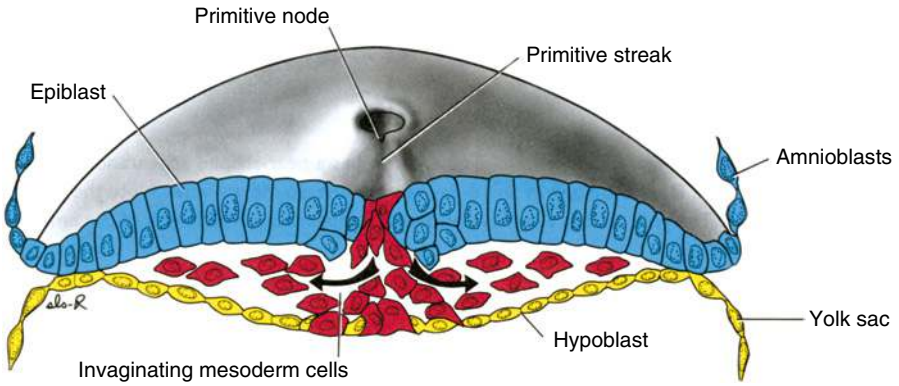


Figure 6.1 Formation of three cell layers. Cross section through the cranial region of the streak at 15 days showing invagination of epiblast cells. The first cells to move inward displace the hypoblast to create the definitive endoderm. Once definitive endoderm is established, inwardly moving epiblast forms mesoderm. (Source: Sadler [22]. Reproduced with permission of Wolters Kluwer.

KEY POINTS: CARDIOGENIC FIELDS

- Myocardial cells are derived from the bilateral cardiogenic or heart fields in the splanchnic layer of the lateral plate mesoderm.
- The heart fields merge to create a cardiac crescent, giving rise to two lineages of cells referred to as the first and second heart fields.
- Cells that contribute to cardiac development originate from the heart field mesoderm, cardiac neural crest, and the proepicardium.

Formation of the heart tube

The primitive linear heart tube is formed during the fourth week of development from the FHF cells with the folding of the embryo. Contrary to originally held beliefs, the cardiogenic fields do not fuse cranially to caudally in a zipper-like fashion. Folding of the embryo and invagination of the foregut brings the lateral portions of the cardiac crescent together that then fuse at the midline from anterior (cranial) to posterior (caudal) to form the ventral part of the heart tube [20, 26] (Figure 6.2 and Figure 6.3C–G). The medial portions of the cardiac crescent will form the dorsal part of the heart tube, which is open to the ventral foregut endoderm and is suspended from the foregut by the dorsal mesocardium. The myocardium of the heart tube is called primitive or primary because, unlike adult working myocytes, the myocytes of the heart tube have few contractile elements, a poorly developed sarcoplasmic reticulum, a low density of gap junctions, and high automaticity [12]. The heart tube has two caudolateral inlets (venous pole) and one craniomedial outlet (arterial pole) [26, 31].

The endocardium is also derived from the splanchnic mesoderm and develops simultaneously with the myocardium in the cardiac crescent. Adjacent endodermal cells release promoters and antagonists of bone morphogenic protein (BMP), fibroblast growth factor (FGF), and wingless-type (WNT) families of growth factors for differentiation of the cardiac crescent cells into cardiomyocytes (29). T-box transcription factors are key regulators of the fate of cardiomyocytes. *Tbx5* and Tbx20 are activators of the chamber program of gene expression. Antagonists of working myocardium gene expression, TBX2 and TBX3, allow the inflow tract, AV canal, and outflow tract myocardium to develop. Tbx1 is expressed in outflow tract precursors and Tbx18 at the venous pole [26]. There are direct correlations between this specific programming and the variants that alter protein function and lead to CHD in humans. Pathogenic germline variants, for example in *TBX1*, have been reported in tetralogy of Fallot [32]. A distinct population of mesodermal cells in each heart field undergoes *de novo* vasculogenesis into two hollow endocardial tubes that join to form a single tube, which becomes enveloped by the cardiomyocytes. The endocardium becomes contiguous with the endothelium of the developing vasculature.

The cardiac jelly, a thick acellular matrix secreted by the myocardium, lies between the myocardium and endocardium. The initial heart tube is therefore a tubular structure with an inner endocardial layer, a middle layer of cardiac jelly, and an outer myocardial layer.

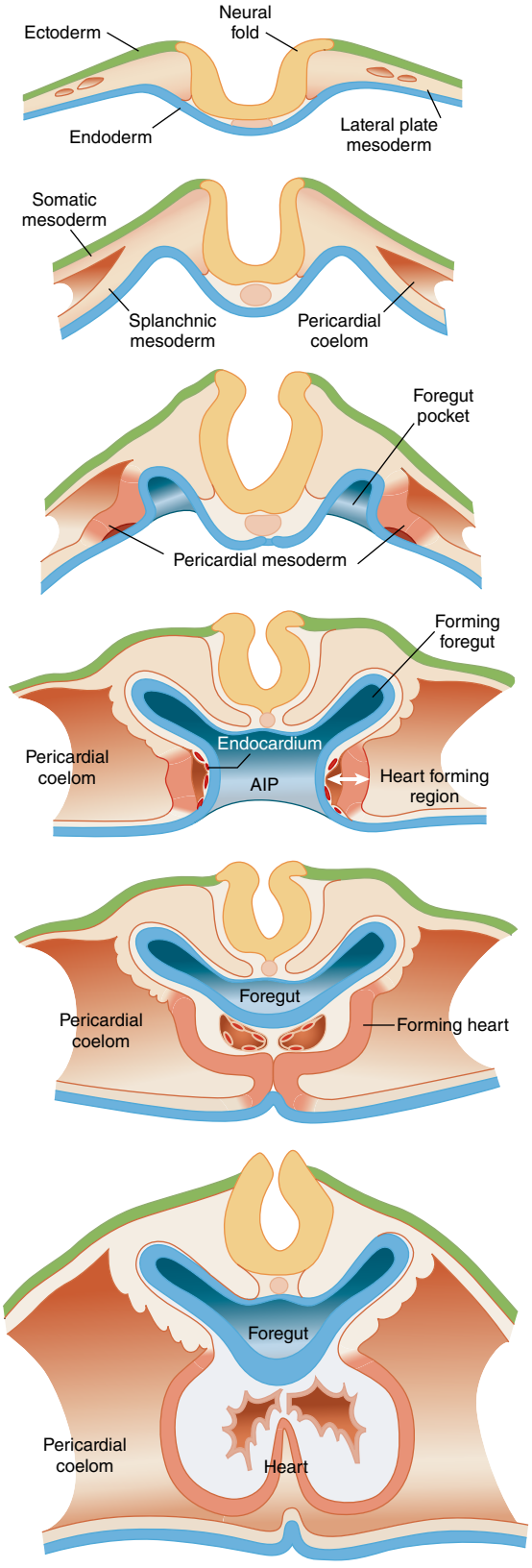


Figure 6.2 Diagrammatic representation of the formation of the heart, foregut pocket, and coelom in the chick embryo. AIP, anterior intestinal portal. (Source: Kirby [23]. Reproduced with permission of Oxford University Press.)

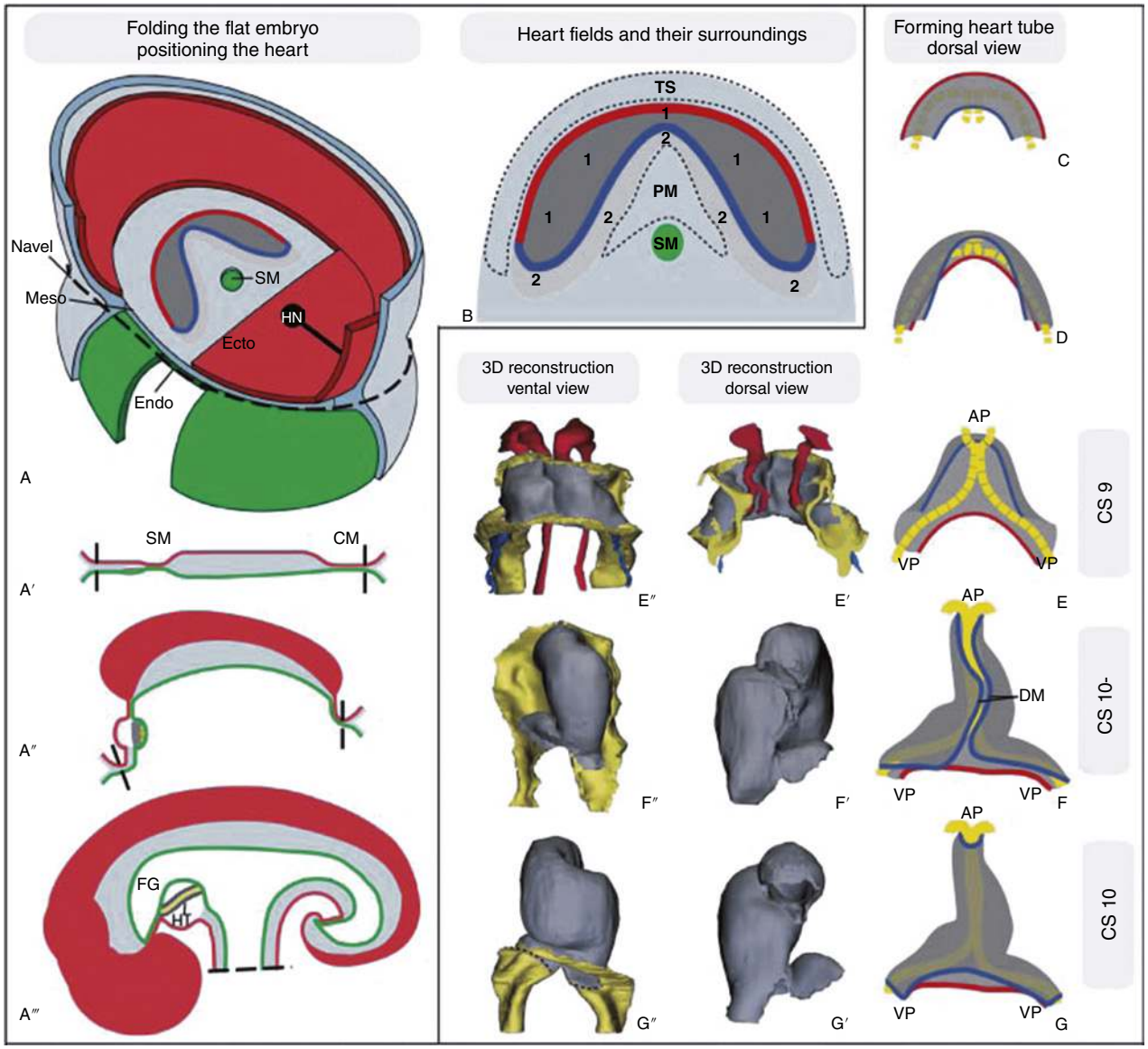


Figure 6.3 Folding of the embryo and formation of the heart tube. (A) The embryo starts as a flat disc containing the three germ layers, the ectoderm (Ecto), mesoderm (Meso), and endoderm (Endo). (A–A‴) With the ongoing folding of the embryo, the embryonic gut that runs from the stomatopharyngeal membrane (SM) to the cloacal membrane (CM) is formed. The heart (HT) becomes positioned ventrally to the foregut (FG), caudally to the head, and cranially to the umbilical cord and transverse septum (TS). HN, Hensen's node or primitive node. (B) Division of the heart-forming field into the first heart field (1), which will give rise to the linear heart tube and the second heart field (2), which will remain in continuity with the first heart field during subsequent development and from which cardiomyocytes are added to the developing heart. In reality, the strict borders drawn here are gradual. PM, pharyngeal mesoderm. (C–G) Formation of the heart tube from a flat horseshoe-shaped cardiac crescent to a tube. Folding of the embryo brings the lateral portions of the cardiac crescent (red line) together to form the ventral part of the heart tube, while the medial portions of the cardiac crescent (blue line) will form the dorsal part of the heart tube, which is suspended from the foregut by the dorsal mesocardium (DM). After the DM closes and the suspension from the foregut is lost, cells of the second heart field can only be added to the heart via the arterial and venous poles (AP and VP, respectively). CS, Carnegie stage (noted along right side of figure). (Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.)

The schematic drawings in older embryology textbooks illustrating the presence of all the cardiac segments in the straight heart tube prior to looping are hypothetical constructions, as most of the segments are added to the primitive heart tube during the looping stages [33].

The primitive atria and ventricles begin to contract around day 22 as the heart tube loops to the right, with circulation through the embryo beginning around day 26. Flow in the valveless heart tube is unidirectional, and because the highest automaticity is found at the venous pole, traveling mechanical waves sweep blood from the venous to the arterial pole [34].

Abnormalities of heart tube formation

Clearly, failure of the heart tube to develop (*acardia*) leads to fetal demise, and as shown in the zebrafish, failure of the bilateral heart fields to fuse results in *cardia bifida* (two separate hearts in lateral positions) [35].

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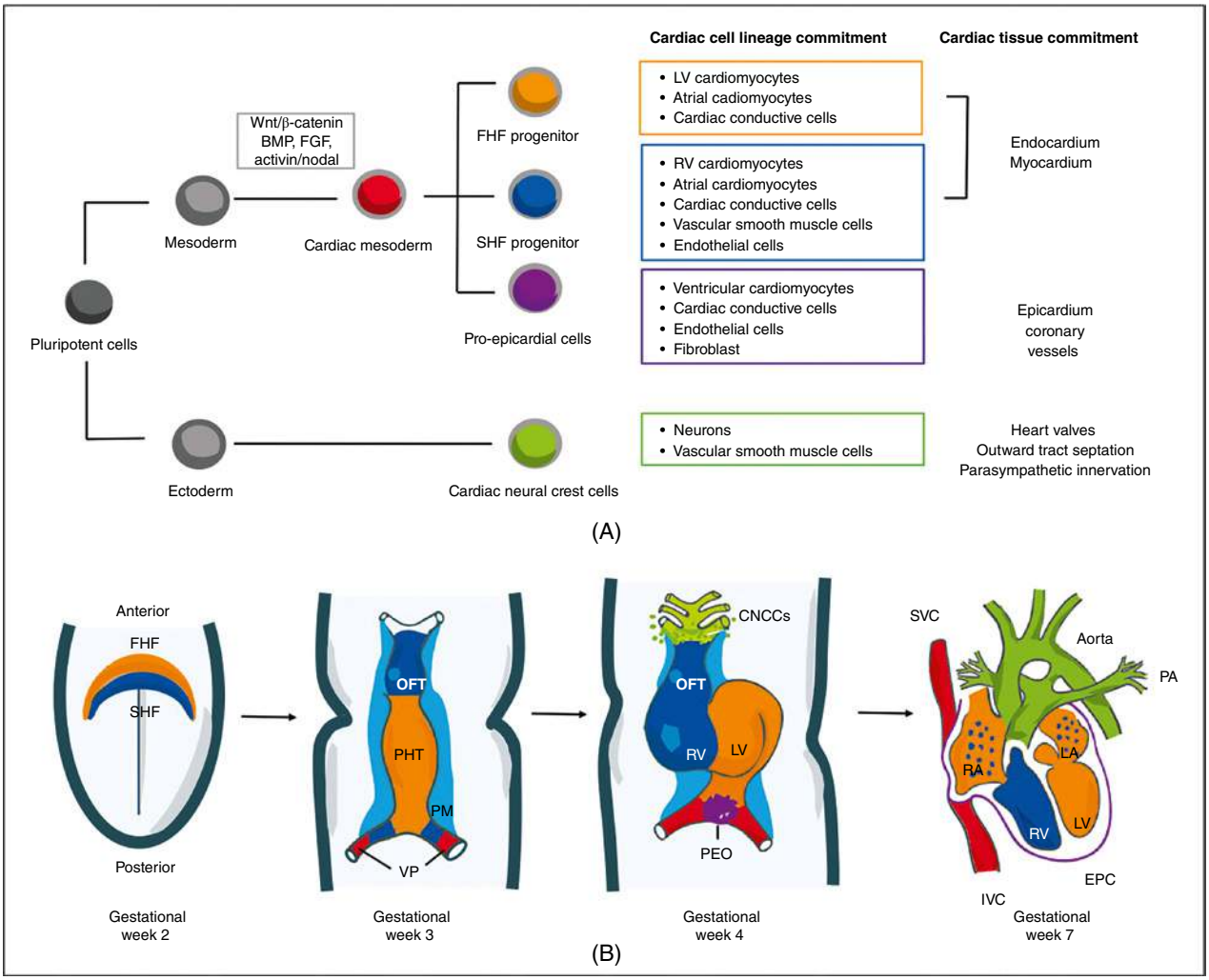


Figure 6.4 Early cardiac development. (A) Cardiac cell lineage and specification during development demonstrate the commitment of pluripotent cells toward mature cardiac cell types within the heart development. (B) Schematic of cardiac morphogenesis in humans. At the second week of gestation, the cardiogenic mesodermal cells migrate toward the anterior side of the embryo to form the FHF or cardiac crescent and SHF that are specified to form specific segments of the PHT, which is patterned along the anteroposterior axis to form the various regions and chambers of the looped and mature heart during weeks 3 and 4. The FHF gives rise to the beating PHT and will eventually give rise to the LV and parts of the right and left atria (RA and LA, respectively). The SHF, located behind the PHT and within the pharyngeal mesoderm by gestational week 3, will contribute to the formation of the RV, parts of the atria and outflow tract, and later to the base of the aorta and pulmonary artery. At gestational week 3, the cells at the venous pole contribute to the formation of the superior and inferior vena cavas (IVC, respectively). By gestational week 4, the cardiac neural crest cells migrate in from the dorsal neural tube, forming smooth muscle cells within the aortic and pulmonary arteries. In addition, the proepicardial organ formed by the proepicardial progenitor cell clusters later contributes to the formation of the epicardium. The four chambers form by the end of week 7. Wnt, Wingles integrated; FGF, fibroblast growth factor; BMP, bone morphogenetic proteins; FHF, first heart field; SHF, second heart field; OFT, outflow tract; PHT, primary heart tube; PM, pharyngeal mesoderm; VP, venous pole; CNCCs, cardiac neural crest cells; LV, left ventricle; RV, right ventricle; PEO, proepicardial organ; SVC, superior vena cava; IVC, inferior vena cava; EPC, epicardium; and PA, pulmonary artery. (Source: Tan [27] / S. Karger AG / CC BY 4.0)

KEY POINTS: FORMATION OF THE HEART TUBE

- The primitive heart tube forms during the fourth week of development.
- Contractile activity initiates around day 22 and circulation through the embryo begins around day 26 of development.
- Failure of the heart tube to develop results in fetal demise.

Cardiac looping

Looping is a crucial process in cardiac morphogenesis that brings the tubular configuration of the primitive circulation into the correct conformation for chamber specification, septation, and the creation of systemic and pulmonary pathways [33, 36]. The heart is the first organ not only to function but also to develop a bilateral asymmetric form. Cardiac asymmetry is attained during the process of looping.

At first, the heart tube is straight in the ventral midline with paired venous limbs at its caudal end and a single arterial outlet connected to the aortic sac and pharyngeal

arch arteries at its cranial end (Figure 6.5) [37, 38]. Looping begins with ventral bending (from dorsal to ventral) and the loss of the dorsal mesocardium, which suspends the heart tube from the foregut (ventral pharynx); these changes transform the straight tube into a curved tube (Figure 6.6). This is followed by a rotation around the craniocaudal axis to the right (*dextro-* or *D-looping*), bringing the left side of the tube to a ventral (front) position, which is seen as a C-shaped loop with the convexity to the right in a ventral, two-dimensional view [33]. At this stage, the junction of the inflow and outflow limbs is at the deepest convexity. Externally, the junction corresponds to the bulboventricular groove, and internally it corresponds to the bulboventricular fold [39]. Subsequent looping produces a ventral, two-dimensional, S-shaped loop (Figure 6.7). The heart tube lengthens as cells are added in a continuous stream to the venous (inflow) and arterial (outflow) poles by the addition of myocardium (cardiomyocytes) and endocardium from the SHF in the adjacent pharyngeal mesoderm. The poles are the only entryway for new cells from the SHF [40]. The ventricular bend then shifts caudally from its cranial position above the atria, and the inflow region shifts cranially, thereby resulting in the convergence of the inflow and outflow poles. After looping, there is rotation (untwisting) of the outflow tract, which results in a leftward shift of the outflow tract. The complex process of cardiac looping is shown in schematic form in Figure 6.8. *Wedging* is the process in which the aorta will come to nestle between the mitral and tricuspid valves and behind the pulmonary trunk (Figure 6.9) [36].

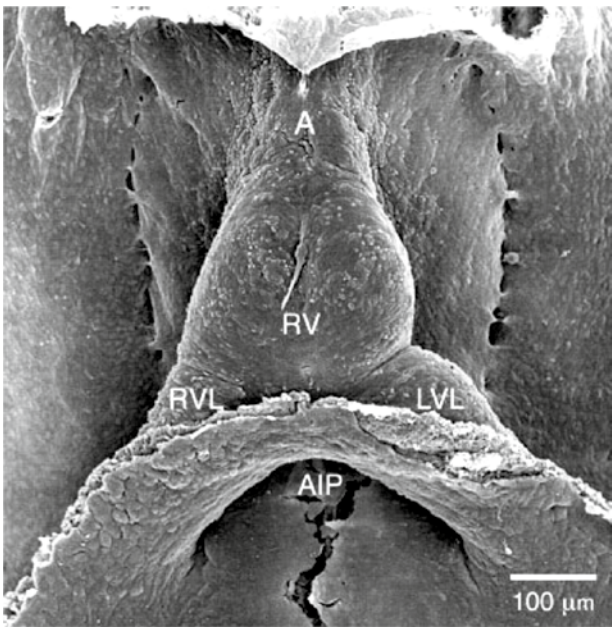


Figure 6.5 Straight heart tube. Scanning electron micrograph of a chick embryo (HH-stage 9), viewed from the front, showing the "straight heart tube" with paired venous limbs at its caudal end and an arterial outlet at its cranial end, which is connected to the aortic sac. A, arterial outlet; AIP, anterior intestinal portal; LVL, left venous limb; RV, primordium of the trabeculated portion of the morphologic right ventricle; RVL, right venous limb. (Source: Männer [33]. Reproduced with permission of John Wiley & Sons.)

When looping is complete, the named segments of the heart (which are extremely variable between authors) are the sinus venosus, common atrium, AV canal, presumptive left ventricle, presumptive right ventricle, conus arteriosus, and truncus arteriosus (frequently referred to as the conotruncus) [41].

Abnormalities of cardiac looping

Cardiac looping is associated with the breaking of the initial bilateral symmetry of the embryo and the establishment of the left-right axis [36, 37]. The left-right axis is established during gastrulation by nodal cilia at the anterior border of the primitive streak. The cilia sweep from right to left, resulting in a leftward flow of extracellular fluid which concentrates a putative secreted factor on the left side of the embryo. Binding of this factor to its receptors triggers asymmetrical gene expression at the node and expression of *Nodal* (a member of the TGFβ family), *Southpaw* and *Lefty2* [25, 42]. The left-sided expression of Nodal is crucial in establishing the left-right axis. Animal models with absent Lefty1 demonstrate thoracic left isomerism and bilateral expression of Nodal, Lefty2, and Pitx2c, implying that Lefty1 restricts expression of Nodal and Lefty2 on the left side and the Nodal and/or Lefty2 signal development [32]. Pitx2c (a member of the homeobox gene transcription factor family) is a key regulator of cardiac left-right patterning that acts downstream of Nodal. PITX2c expression on the left side persists long after Nodal expression [26]. Left ventricle chamber identity is associated with HAND1 expression and right ventricular chamber identity with HAND2 expression [43].

Left-right signaling pathways determine not only the direction of looping and the topology of the future ventricular chambers but also the proper development of the atria, the arterial and venous poles, and the systemic vasculature. Abnormalities in left-right patterning increase the incidence of cardiac malformations in both D- and L-loop hearts; typical examples include mirror imagery, atrial isomerism, discordant connections, and heterotaxy [44]. The left-right signaling cascade is hierarchical because abnormalities high in the cascade result in randomization of situs, whereas abnormalities lower down, which are associated with tissue-specific signaling, produce discordant connections [26].

Normal cardiac looping to the right, referred to as *dextro-looping* or *D-looping*, positions the right ventricle towards the right side and leaves the heart lying predominantly in the left hemithorax with a leftward apex (*levocardia*) (Figure 6.10, left panel). *Situs solitus* refers to normal looping with the liver, stomach, and spleen in their normal positions. Rotation around the craniocaudal axis to the left results in a *levo-loop* (*L-loop*) heart (Figure 6.10, right panel), in this position the right ventricle is positioned toward the left and the left ventricle toward the right. *Congenitally corrected transposition of the great arteries* (CCTGA) arises when the heart (ventricle) loops to the left but the atria and outflow receive correct left-right signals, resulting in both AV and ventriculoarterial (VA) discordance. CCTGA can also occur when the heart loops to the right with inversion of the atria and VA discordance. *Situs inversus totalis* refers to an L-loop heart with mirror-image reversal, which means

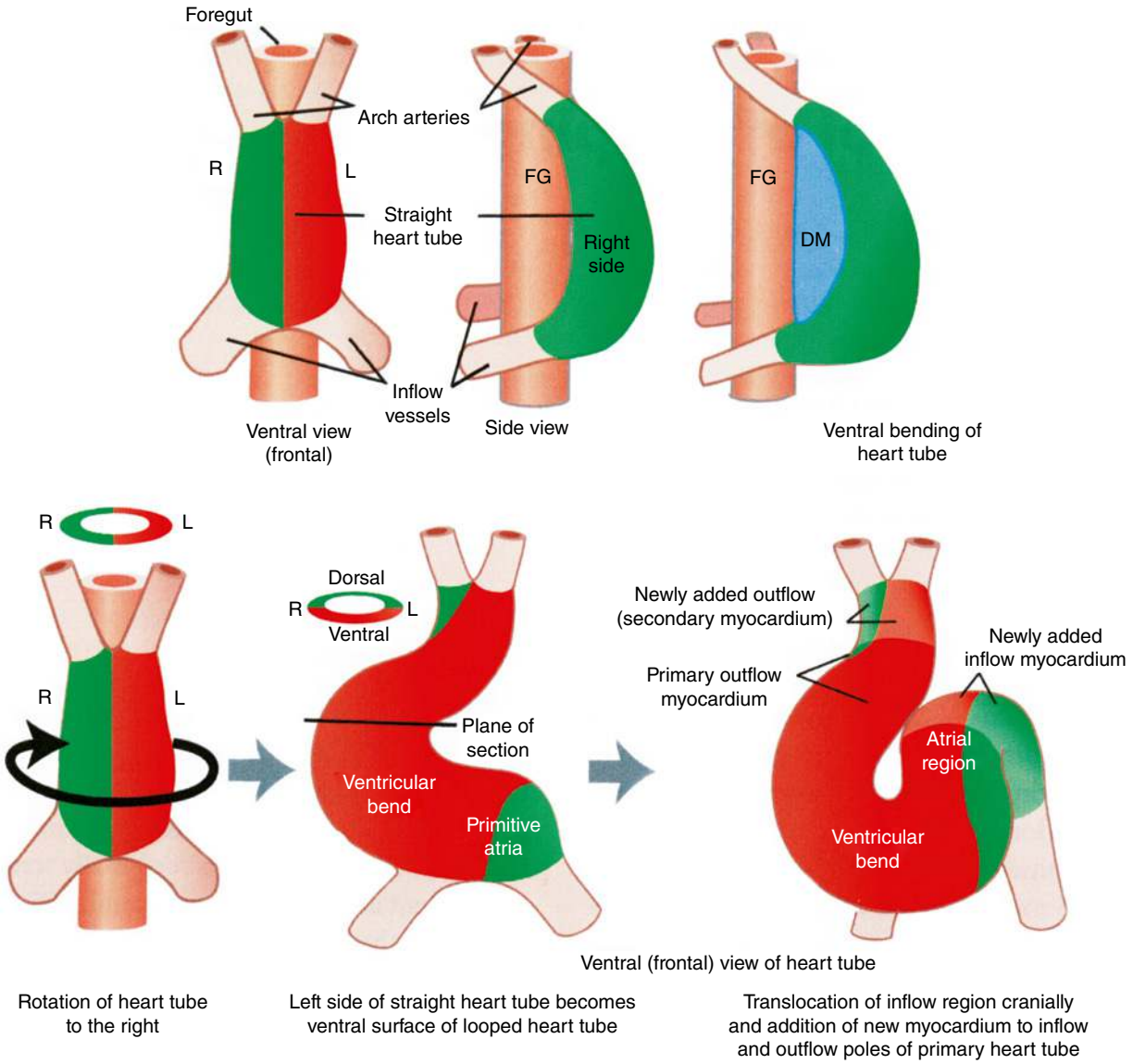


Figure 6.6 Steps in looping of the heart tube. The heart tube forms ventral to the foregut and is open to it at first. Then the heart tube is suspended at its nascent inner curvature from the ventral foregut by the dorsal mesocardium which quickly disappears. Ventral bending occurs first, followed by rotation to the right which brings the left side of the tube to the front and the inner curvature to the left side. Subsequent looping to form the S-shaped loop involves the addition of cells at the inflow and outflow poles. DM, dorsal mesocardium; FG, foregut. (Source: Kirby [23]. Reproduced with permission of Oxford University Press.)

the heart lies predominantly in the right hemithorax with a rightward apex (*dextrocardia*) and there is a mirror-image reversal of the liver, stomach, and spleen. *Mesocardia* refers to a midline heart with the apex pointing inferiorly or anteriorly. Mesocardia and dextrocardia can be associated with a normal or abnormal arrangement of cardiac structures. *Atrial isomerism* refers to a bilaterally symmetrical pattern of the atrial appendages (i.e. bilateral leftness or rightness) and is usually associated with severe complex cardiac malformations. Abnormal PITX2c expression results in both atria developing right atrial appendages, establishing a role of PITX2c in the differentiation of atrial sidedness [45]. *Mixed situs* occurs when some organs, or components thereof, have normal situs and others have situs inversus. This usually results in complex heart defects known as *heterotaxia* or *heterotaxy* syndromes (discussed later in the chapter).

KEY POINTS: CARDIAC LOOPING

- Cardiac looping represents a crucial process in cardiac morphogenesis that determines the shape of the heart.
- The process of cardiac looping is complex, resulting in right-left asymmetry in the embryo.
- Normal cardiac looping is to the right, referred to as dextro- or D-looping; abnormal looping to the left results in Levo- or L-looping.

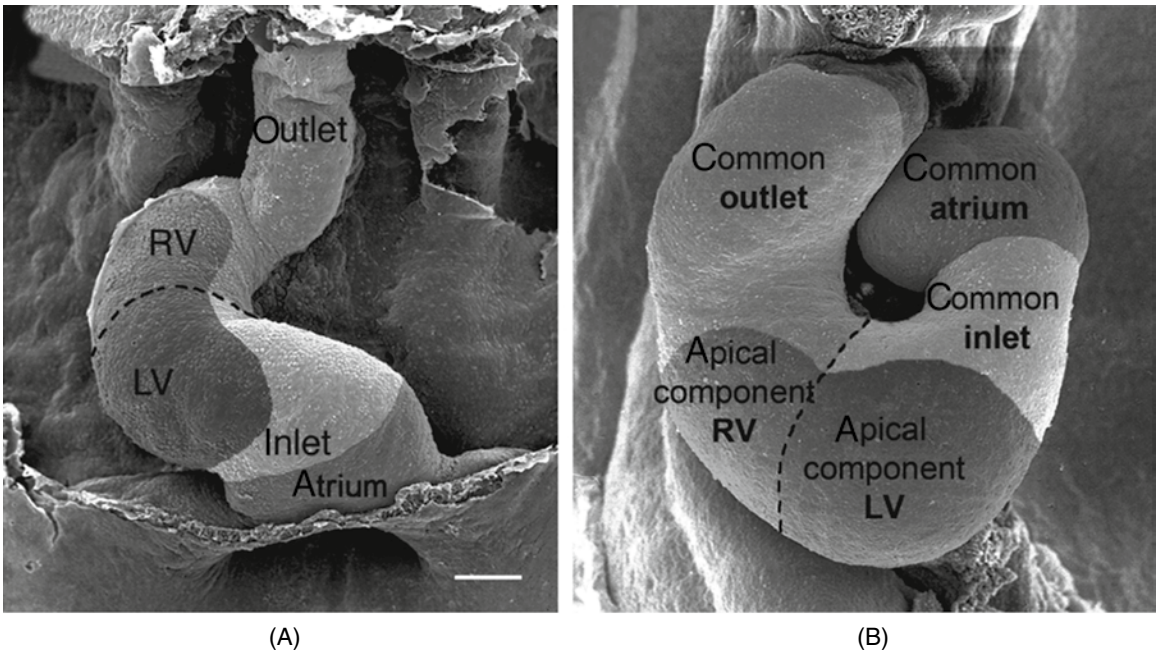


Figure 6.7 Looping morphogenesis. Scanning electron micrographs of embryonic chick hearts, viewed from the front, showing the main positional changes of the developing heart chambers of higher vertebrate embryos during cardiac looping. (A) "C"-shaped loop at early stages (HH-stage 12). (B) "S"-shaped loop at advanced stages (HH-stage 17/18) of cardiac looping. RV, right ventricle; LV, left ventricle. (Source: Männer [37]. Reproduced with permission of Elsevier.)

Cardiac septation

Cardiac septation begins after looping of the heart tube. It consists of four contemporaneous processes that occur between 27 and 37 days of development, dividing the heart into four chambers and creating separate systemic and pulmonary circulations [22]. Septation is attributable to the muscular septa in the atrial and ventricular chambers, the AV endocardial cushions, the outflow tract endocardial cushions, and the dorsal mesenchymal protrusion. *TBX2/3* and *BMP2/4* are important repressors of chamber-specific genes like *ANF* to allow for the development of the nonchamber myocardium [25]. Indeed, deletion of either *Bmpr1a* or *Tbx2* leads to the development of additional myocardial connections [46, 47].

Atrial septation

Atrial septation takes place in phases to maintain right-to-left atrial shunting and involves the septum primum, septum secundum, and AV canal (AVC) septum. The *primary atrial septum* (septum primum) grows as a muscular crescent from the craniodorsal wall of the atrium on the right of the pulmonary

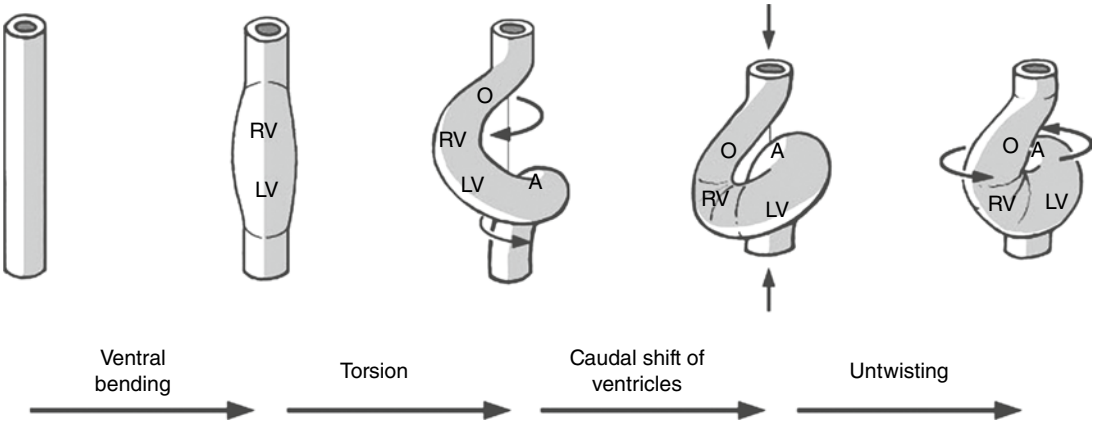


Figure 6.8 Ventricular looping. Schematic drawing (frontal views) of the four components of normal ventricular looping: (1) ventral bending transforms a straight tube into a curved tube whose outer curvature is formed by its ventral wall; (2) torsion around its original cranio-caudal axis transforms a curved tube into a helically wound loop which appears C-shaped in frontal views; (3) caudal shift of the ventricular segment; (D) untwisting is characterized by ventral and leftward shift of the proximal outflow tract, ventral shift of the primitive right ventricle, and rightward shift of the atrioventricular canal. A, common atrium; LV, embryonic left ventricle; O, outflow tract; RV, embryonic right ventricle. (Source: Männer [33]. Reproduced with permission of John Wiley & Sons.)

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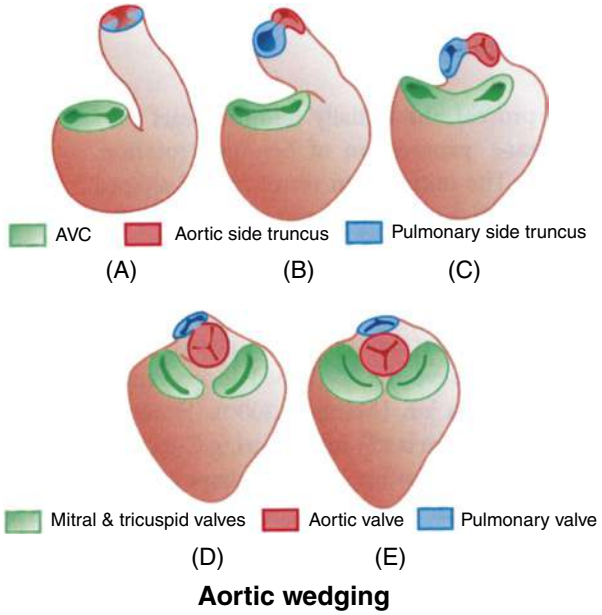


Figure 6.9 Steps in aortic wedging (A–E). The aortic side of the outflow tract nestles between the mitral and tricuspid valves as the outflow myocardium is remodeled. AVC, atrioventricular canal. (Source: Kirby [23]. Reproduced with permission of Oxford University Press.)

pit toward the AV endocardial cushions (Figure 6.11). The leading edge of the septum primum is covered by a mesenchymal cap produced by the endothelial-to-mesenchymal transformation (EMT) of the endocardium covering the septum [40]. EMT is a complex biologic process whereby endothelial cells lose their specific phenotype and evolve into cells with a mesenchymal phenotype that includes spindle-shaped elongated cell morphology, loss of cell-cell junctions and polarity, and acquisition of functions such as cellular motility, contractility, and invasiveness [48]. This mesenchymal cap is continuous with the protrusion of the dorsal mesocardium (dorsal mesenchymal protrusion) and the dorsal (superior) and ventral (inferior) AV endocardial cushions [26]. The communication between the leading edge of the septum primum and the AV cushions is known as the *primary atrial foramen* (ostium primum), which closes when the septum primum becomes contiguous with the fused dorsal and ventral AV endocardial cushions. Communication between the left and right atria is maintained by the detachment of the septum primum from the roof of the atrial cavity to produce a secondary atrial foramen (ostium secundum) [49]. The *secondary atrial septum* (septum secundum) is formed by the folding of the dorsal wall between the primary atrial septum and the left leaflet of the sinoatrial valve. The septum secundum does not fuse with the AV cushions but remains open as the *foramen ovale*. The cranial portion of the septum primum remains as a flap valve, which fuses with the edges of the foramen ovale after birth to form the fossa ovalis [40]. The muscular septum between the inferior rim of the fossa ovalis and the AV valves is called the AVC septum.

Early in development, the *venous pole* of the heart has two channels (the left and right horns of the sinus venosus), returning blood from the embryo (via the cardinal, vitelline, and umbilical veins) to the sinus venosus and common atrium. During the convergence phase of looping, the common atrium

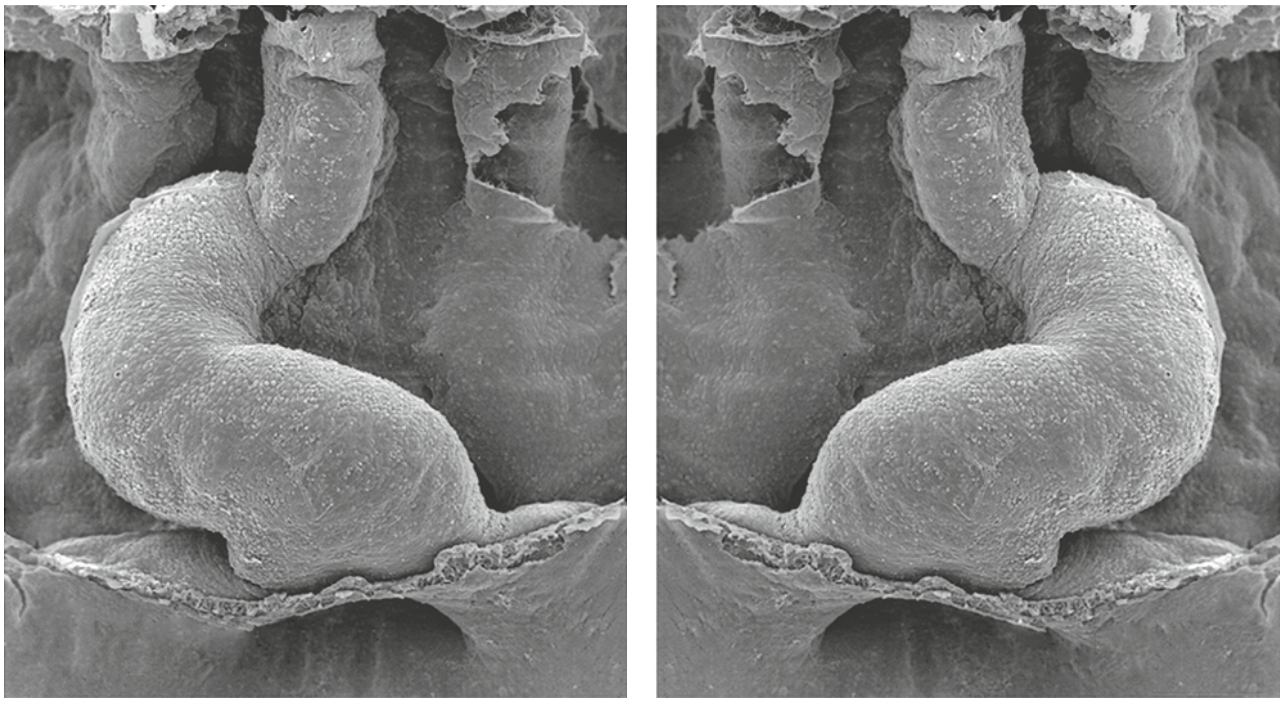


Figure 6.10 Handedness of the cardiac loop. Scanning electron micrographs of embryonic chick hearts, viewed from the front, showing the so-called D-loop (dextral-loop) (A) and L-loop (levo-loop) (B) configurations ("C-shaped" loops; HH-stage 12). (Source: Männer [37]. Reproduced with permission of Elsevier.)

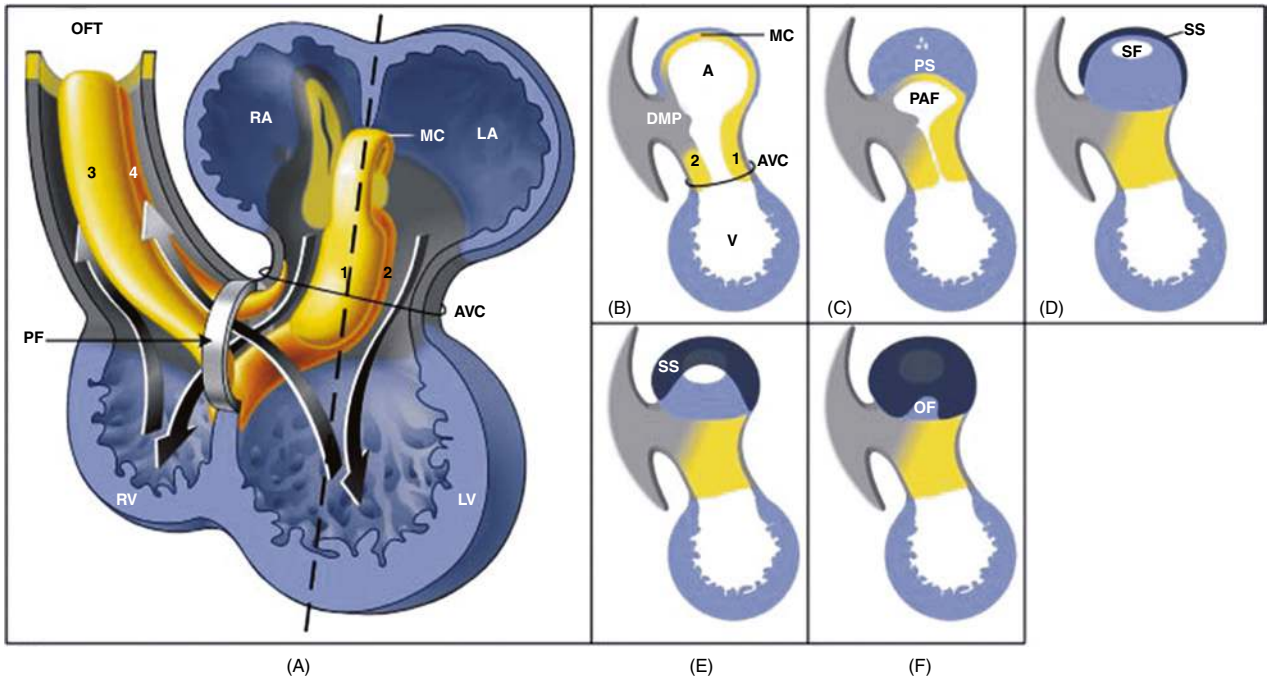


Figure 6.11 Schematic drawing illustrating septation of the atria and primary foramen. (A) Chamber-forming heart with the atrioventricular canal (AVC) and outflow tract (OFT) cushions and ridges. The two arrows going down through the AVC into the ventricle represent blood flow during diastole. The two arrows pointing toward the OFT represent blood flow during systole. Note that the primary foramen (PF) is the crossroad of the blood running from the right atrium (RA) to the right ventricle (RV), and the blood running from the left ventricle (LV) to the OFT. (B–F) Sagittal sections at the level of the dotted line in (A). (B) The ventral and dorsal endocardial cushions (1 and 2, respectively) are growing toward each other. (C) The primary atrial foramen (PAF, ostium primum) is closing due to ingrowing of the primary atrial septum (PS, septum primum), with its mesenchymal cap (MC), the dorsal mesenchymal protrusion (DMP), and the endocardial cushions. (C, D) In the PS, small holes appear and merge to form the secondary foramen (SF, ostium secundum). (D–F) The secondary septum (SS, septum secundum) grows to the right side of the PS covering the SF and the rest of the PS, and leaving at the right surface of the atrial septum only the oval fossa (OF) uncovered. A, atrium; LA, left atrium; V, ventricle; 3 and 4, septal and parietal outflow tract ridges, respectively. (Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.)

expands to the right and left, forming two lateral pouches that will become the right and left atrial appendages [33, 50]. Remodeling results in the sinoatrial junction shifting to the right side of the common atrium. The right horn of the sinus venosus and the sinoatrial junction become incorporated into the dorsal (back) wall of the right atrium (Figure 6.12). The sinoatrial junction has left and right craniocaudally oriented valves (venous valves) that meet cranially to form the septum spurium [50]. As the distal portion of the left superior cardinal vein regresses (and thereby absent left superior vena cava), the left horn of the sinus venosus becomes smaller and is incorporated into the developing AV groove to become the coronary sinus. The dorsal (back) wall of the left atrium is also formed by the incorporation of the pulmonary vein and its surrounding myocardium [39, 50].

Defects in atrial septation

The most common cause of an atrial-level shunt is *a secundum atrial septal defect* (ASD), which is located within the region of the fossa ovalis. It is usually due to a deficiency of the septum primum but, in rare cases, it can be caused by the deficiency of the septum secundum [51].

Failure of the septum primum and septum secundum to fuse completely during infancy results in a *patent foramen ovale* (PFO). As long as the left atrial pressure exceeds the right atrial pressure and the flap valve is large enough to cover the boundaries of the fossa ovalis, the foramen remains functionally closed (probe patent foramen).

An *ostium primum defect* results from the failure of the septum primum to fuse with the endocardial cushions. The defect is outside the confines of the fossa ovalis and extends from the inferior limbus of the fossa ovalis to the crest of the interventricular septum. An ostium primum defect is part of the family of AVC defects, also referred to as AV septal and endocardial cushion defects and may occur in isolation or in association with other abnormalities of the AV junction.

A *sinus venosus defect* occurs in the area derived from the embryologic sinus venosus (posterior aspect of the right atrium) so is not strictly a defect in the atrial septum. It is an interatrial communication caused by a deficiency of the common wall between the superior vena cava (SVC) and the right-sided pulmonary veins [52, 53]. The most common location for this defect is between the right upper pulmonary vein and the cardiac end of the SVC type, although in rare cases the right lower and/or middle pulmonary veins and more caudal atrial wall are involved (inferior vena cava [IVC] type) [51].

A *coronary sinus defect* occurs because of unroofing of the normal course of a persistent left anterior cardinal/superior caval vein into the left horn of the sinus venous, i.e. the tissue between the coronary sinus and the left atrium is either partially or completely absent (unroofed) resulting in

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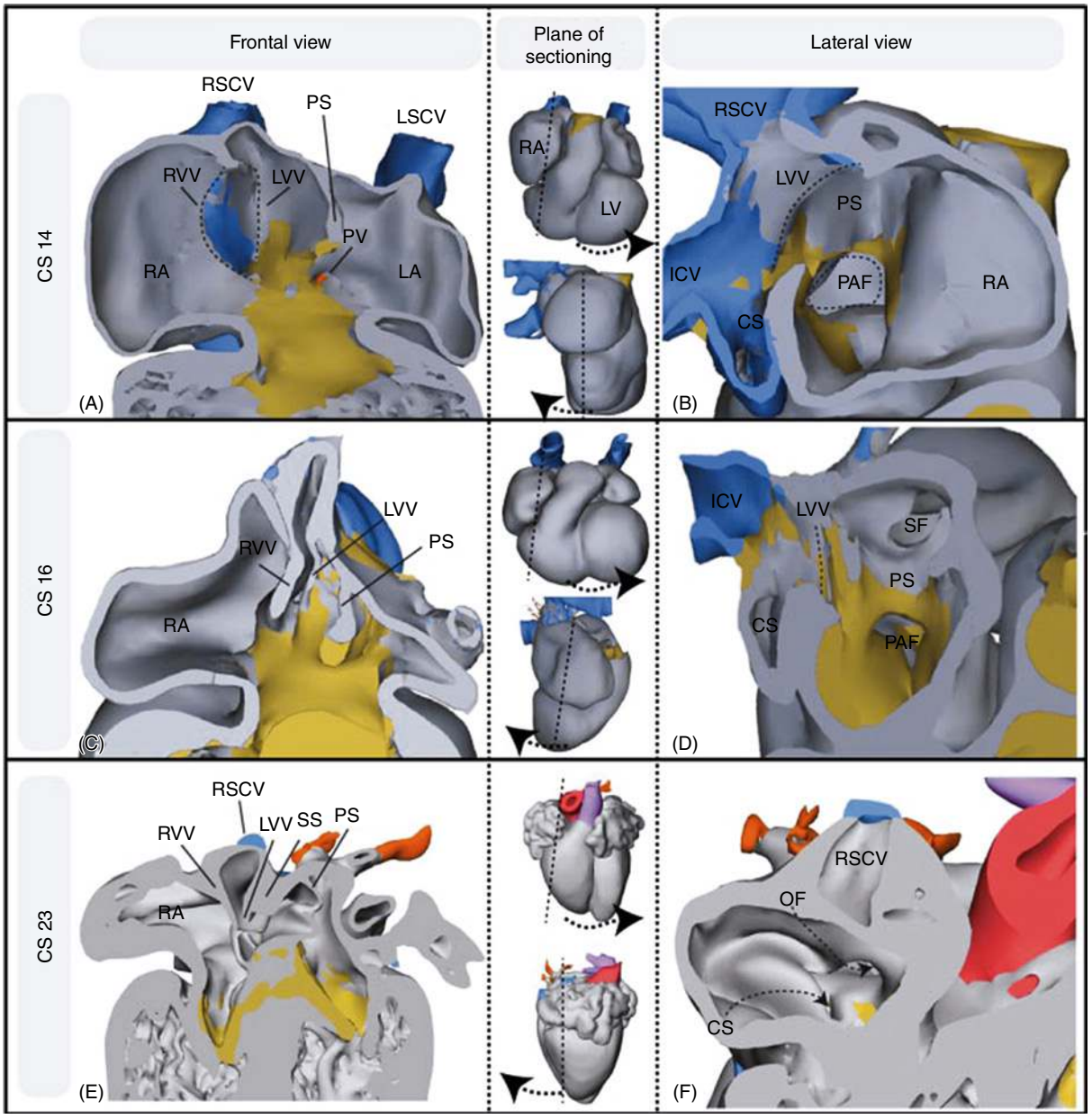


Figure 6.12 Formation of the venous pole. (A–F) Cross-sections of three-dimensional (3D) reconstructions of human hearts (gray, myocardium; blue, systemic veins; orange, pulmonary veins; yellow, cardiac mesenchyme). (A, B) Developing right and left atrium (RA, LA); the RA is connected to both the right superior (RSCV) and inferior caval vein (ICV) as well as the left superior caval vein (LSCV), via the coronary sinus (CS). At this stage, the entire systemic venous pole is connected to the right atrium through one orifice, flanked by the left and right venous valves (LVV and RVV). The primary septum (PS) is growing to the right of the opening of the pulmonary vein (PV). (C, D) The RSCV and CS are still connected to the atrium via a single orifice, which has now been muscularized. The secondary foramen (SF) appears in the primary septum. (E, F) All veins connect separately to the atrium via myocardialized orifices. The primary atrial foramen (PAF) is closed, and the secondary septum (SS) is growing between the PS and the LVV, which is already partially fused to the secondary septum. The RVV can now be separated into a part that flanks the CS and a part that flanks the RSCV, the future Thebesian and Eustachian valves, respectively. OF, oval foramen; CS, Carnegie stage (noted on the left margin of figures). (Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.)

communication between the right and left atria via the coronary sinus orifice [53]. The left-to-right shunt causes enlargement of the coronary sinus orifice.

A *common atrium* is caused by the absence of the septum primum, septum secundum, and atrial portion of the AVC septum and is usually associated with the heterotaxy syndrome [51].

Ventricular septation

After looping of the heart tube occurs, differentiation and re-initiation of cell division by the primary myocardium of the outer curvature cause the ventricles to expand caudally in a pouch-like fashion on either side of the bulboventricular groove (Figure 6.13). De Boer and colleagues [54] have shown that growth of the trabeculae occurs by cellular

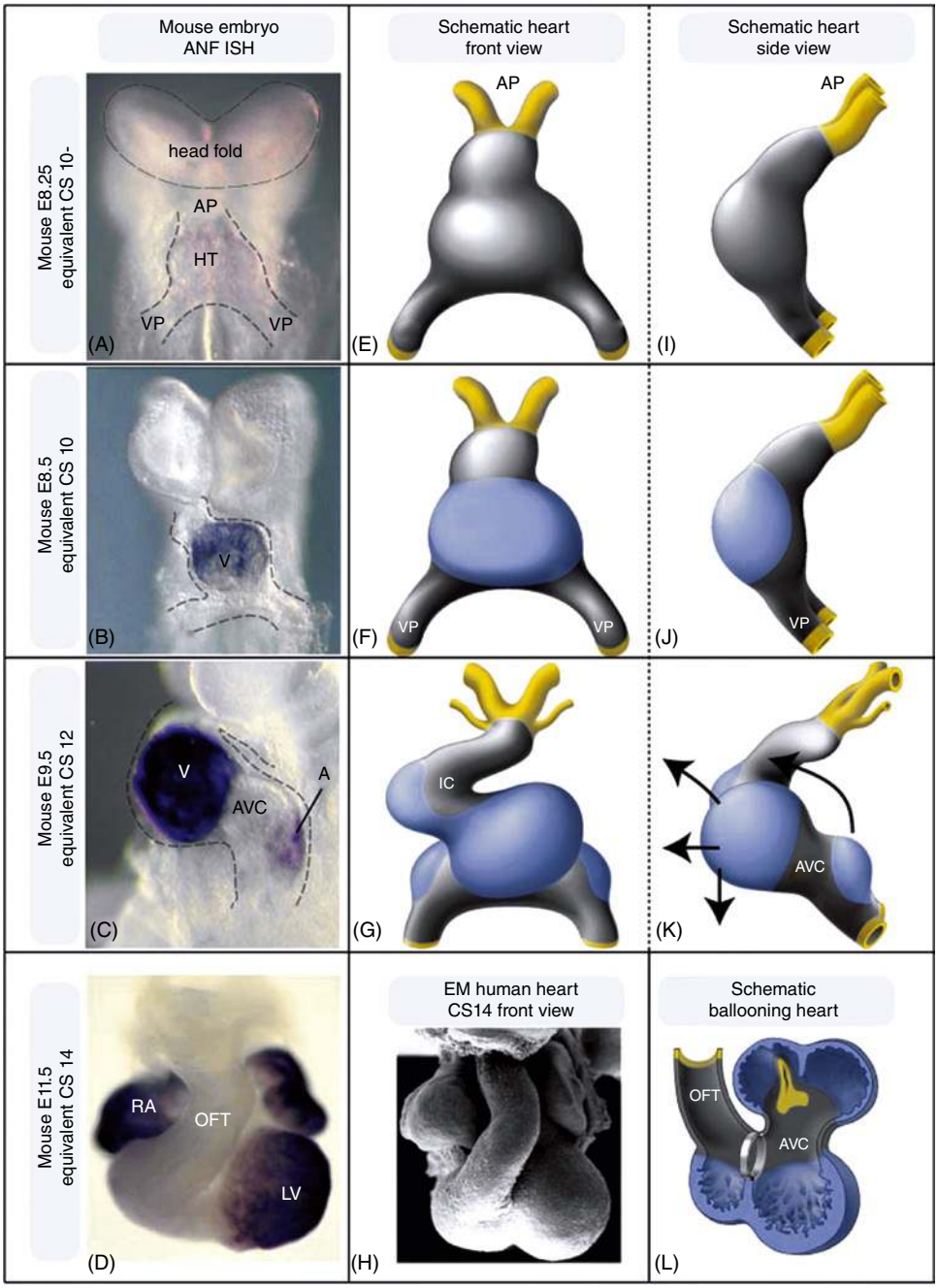


Figure 6.13 Formation of the cardiac chambers. (A–D) Developmental series of mouse embryos. Whole-mount RNA ***in situ*** hybridization for the embryonic chamber marker atrial natriuretic factor (ANF) is used as a marker for differentiation into chamber myocardium. (E–G) and (I–L) Schematic drawings of these chamber-forming hearts. Gray, primary myocardium; blue, chamber-forming myocardium; arrows in K indicate the expansion of the chambers eventually leading to the adult configuration, with the ventricles positioned ventro-caudally to the atria. (H) Electron micrograph of a CS14 human heart, demonstrating the similarity with the mouse E11.5 heart and the schematic shown in (L). For didactic purposes, in the schematic in (L), the outflow tract is hinged toward the right side, ***in vivo*** it is positioned ventrally to the heart, as depicted in (D) and (H). (A, E, I) The heart tube (HT) consists solely of the primary myocardium from the venous (VP) to the arterial pole (AP). (B, F, J) The first chamber to start ballooning is the embryonic ventricle (V) at the outer curvature of the heart. (C, G, K) The heart tube has started to loop and acquire an S shape. An embryonic left and right ventricle are now visible. The atria (A) also start to balloon towards the left and right side. The myocardium of the outflow tract (OFT), inner curvature (IC), and atrioventricular canal (AVC) remain as the primary myocardium. RA, right atrium; LV, left ventricle; CS, equivalent Carnegie stage noted in the left margin of figures. (Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.)

proliferation at the bases, causing the ventricles to expand or "balloon outward" (ballooning model of chamber formation). The disappearance of the cardiac jelly results in the formation of trabeculations on the luminal side, producing a spongy-type myocardium. Compact myocardium forms later when epicardially derived fibroblasts infiltrate the epicardial side, at which time proliferation in the trabeculations ceases.

The *muscular* portion of the interventricular septum is formed by apposition and merger of the medial walls of the expanding ventricles, with cells added mainly from the adjacent left ventricular free wall [22]. The septum represents the least changed part of the lumen of the embryonic heart and the superior portion expresses a transcriptional repressor, TBX3 [55]. It is initially crescent-shaped, extending from the ventral (inferior) AV cushion posteriorly to the dorsal (superior) AV cushion anteriorly. The space between the free rim of the muscular septum and the fused AV cushions is the *primary interventricular foramen*. Although the primary interventricular foramen allows for communication between the primitive left and right ventricles, initially blood from the primitive atrium can only reach the primitive right ventricle via the interventricular foramen (Figure 6.11). It is only after the AV junction develops that the right atrium will communicate directly with the right ventricle. Closure of the interventricular foramen occurs by fusion of three tissue components: the dorsal (superior) and ventral (inferior) AV endocardial cushions, the muscular interventricular septum, and the endocardial cushions of the outflow tract (conal cushions). The septal conal cushion extends deep into the future right ventricle to merge with the dorsal AV cushion and the rightmost edge of the developing muscular septum [56]. The site where these three structures fuse constitutes the *membranous* part of the ventricular septum. The ventricular septum is fully closed at an estimated gestational age of 9 1/7 weeks [57].

Defects in ventricular septation

A ventricular septal defect (VSD) is an opening or hole in the interventricular septum [58]. It may be found in isolation or may co-exist with other congenital cardiovascular anomalies. Because the ventricular septum is composed of three components (muscular, AVC endocardial cushions, and outflow tract [conal] cushions), defects at the ventricular level may result from a deficiency of one or more of these structures and/or from their malalignment. The classification of VSDs can be confusing because of different nomenclatures used by various authors [59].

The most common VSDs are those that occur in the *muscular* portion of the interventricular septum [2]. This type of VSD is surrounded by a rim made completely of muscle. They are often multiple and may be located anywhere in the muscular septum (apical, anterior, mid, or posterior).

The *membranous septum* is a small, translucent structure. It is adjacent to the anteroseptal commissure of the tricuspid valve when viewed from the right side and is located below the noncoronary leaflet of the aortic valve when viewed from the left. Small defects may spontaneously close after birth due to the presence of the surrounding fibrous tissue (also referred to as aneurysmal tissue). Defects that extend beyond the boundaries of the membranous septum are called *para-* or *perimembranous* defects. Membranous VSDs are closely associated with the bundle of His, increasing the risk of causing conduction disturbances and complete heart block during the repair.

A *conoventricular* or *subaortic defect* is situated between the conal and muscular portions of the ventricular septum and is also close to the bundle of His. This defect is often related to malalignment of the muscular and conal portions of the ventricular septum.

A *subpulmonary*, *conal*, *supracristal*, or *doubly committed subarterial* defect is located in the outflow tract (conal septum) just below the pulmonary valve. Fibrous continuity between the aortic and pulmonary valves is frequently present. The aortic valve (right cusp or non-coronary cusp) may prolapse into the defect, which may result in aortic regurgitation.

An *inlet* or *AVC-type VSD* occurs when the inferior endocardial cushion does not fuse with the muscular component of the ventricular septum. The defect is located in the *inlet* portion of the right ventricle beneath the tricuspid valve and may be perimembranous or muscular [59]. The origin of the AV node and the course of the AV bundle (His) differ with respect to the normal heart, increasing the risk of injury during surgical repair.

A *common* or *single ventricle*, defined as the presence of two AV valves with one ventricular chamber or a large dominant ventricle with a diminutive or hypoplastic opposing ventricle may result from various mechanisms. The pathology may be due to the arrest of or a defect in interventricular septation or from poor alignment of the common AV valve with the ventricles [60]. A wide spectrum of functional single ventricles is recognized. These ventricles include double-inlet single ventricle (usually left), defects resulting from atresia or absence of either the right or left AV valves, such as tricuspid atresia, mitral atresia (part of hypoplastic left heart syndrome [HLHS]), those with an atretic semilunar valve (HLHS, pulmonary atresia with intact ventricular septum), unbalanced common AVC defects, and some forms of double-outlet right ventricle.

Atrioventricular canal septation and AV valve development

The cardiac jelly at the AV junction (and outflow tract) forms into mounds by the myocardial synthesis of the extracellular matrix. The endocardial cushions arise from the cells of the endocardium overlying these swellings that invade the cardiac jelly and undergo EMT into fibroblast-like mesenchymal cells [61, 62]. AV canal and outflow tract myocardium produce BMPs that signal through the cardiac jelly to the endocardium. As a result, TGF-beta and Notch signals regulate the EMT of the cushions [63]. Prior to valve formation, the endocardial cushions and underlying myocardium prevent the backflow of blood. Four cushions develop in the AVC: the inferior (ventral) and superior (dorsal) cushions located centrally and two smaller cushions on the lateral walls (left and right). Central fusion of the inferior and superior cushions forms the AV septum, thereby separating the AVC into the left (mitral) and right (tricuspid) orifices [64]. The *atrial portion of the AV septum* extends from the level of the valve annuli to fuse with the primary atrial septum, whereas the *ventricular portion of the AV septum* extends from the level of the valve annuli to form the inlet portion of the interventricular septum. The AVC expands to the right, as does the right ventricle, to allow for direct communication between the presumptive right atrium and the presumptive right ventricle (Figure 6.11).

The septal leaflet of the tricuspid valve and the anterior leaflet of the mitral valve are derived from the fused inferior and superior endocardial cushions, whereas the mural leaflets are derived from the lateral cushions [65]. Mature AV

valves and the subvalvular apparatus are formed by cavitation and remodeling of the cushions and excavation of the underlying ventricular myocardium to form leaflets and chordae tendinae (Figure 6.14) [65, 66]. Late in development, the primitive leaflets undergo lengthening and delamination with the disappearance of the myocardial layer.

After the endocardial cushions have fused, the fibroblast-like cells of the cushions are replaced by myocardial cells in a

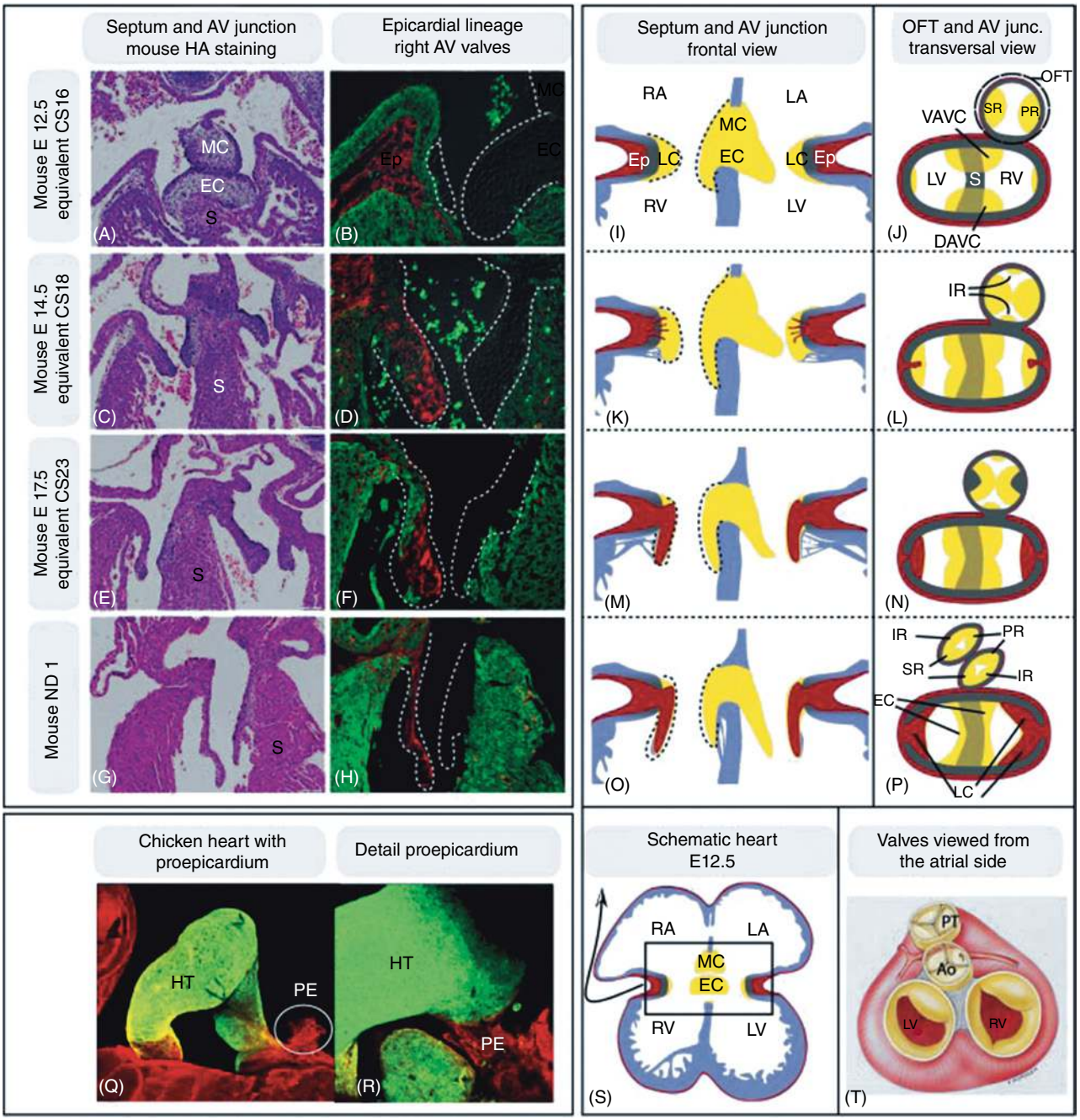


Figure 6.14 Development of the atrioventricular (AV) and outflow tract (OFT) valves and their contributing tissues. (A–H) Sections through mouse hearts in a plane comparable to the schematic heart in panel (S). (B, D, F, H) The lineage contributions of the epicardium is displayed at different developmental stages. The epicardial lineage marker WT1 was used; epicardial lineage is depicted in red, myocardium in green. (I–P) Schematic drawings of valve development in both the atrioventricular canal and outflow tract. Red, epicardium (Ep); gray, primary myocardium; and yellow, endocardial cushion tissue (EC). Note that in the outflow tract the cells are primarily neural crest-derived and not endocardial-derived as in the AV canal. (P) The contribution of the different cushions and ridges to the eventual valves (panel T) is depicted. (Q, R) Display the proepicardium (PE) in a 3-day-old chick embryo. The PE is attached to the heart tube (HT) and spreads out to form the epicardium. Ao, aorta; DAVC, dorsal AV cushion; IR, intercalated ridge; LA, left atrium; LC, lateral cushion; LV, left ventricle; MC, mesenchymal cap; PR, parietal ridge; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; S, septum; SR, septal ridge; VAVC, ventral AV cushion. Equivalent Carnegie stage (CS) is noted in the left margin of the figures. (Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.)

process called myocardialization. Fusion of the nonmyocardial mesenchymal cushions and myocardialization create part of the atrial septum, ventricular septum, and conal septum, as well as the substrate for the crux of the heart.

Defects of the AVC

The endocardial cushions of the AVC contribute to the formation of the atrial septum, the ventricular septum, and the mitral and tricuspid valves. They form between the atrium and ventricle in a vascular endothelial growth factor-dependent manner. Variants in vascular endothelial growth factor (VEGF) are implicated as a modifier gene in valvuloseptal CHD [67]. Endocardial cushion-derived structures can have varying degrees of abnormalities producing a spectrum of lesions called endocardial cushion defects (as previously noted, they are also referred to as AVC or AV septal defects). Failure (incomplete or complete) of the endocardial cushions to fuse creates a defect in the AV septum.

A *partial (incomplete)* AVC defect results from incomplete fusion of the superior endocardial cushion with the septum primum and consists of an *ostium primum ASD* with distinct left and right valve annuli, and frequently there is a mitral valve cleft with varying degrees of regurgitation [68]. A *transitional* AVC defect is typically an ostium primum defect with a very small to moderate (restrictive) inlet VSD, which is often occluded by AV valve tissue. Although there are two separate orifices, the valves are abnormal [68]. Lack of fusion of the superior and inferior endocardial cushions leads to a *complete AVC (CAVC)* defect comprising an ostium primum ASD, a non-restrictive VSD just below the AV valve (inlet VSD), and a common AV valve annulus that bridges both the left and right sides of the heart, i.e. the valve leaflets are shared between the left and right ventricles and are not adherent to the crest of the ventricular septum. In the normal heart, the septal leaflet of the tricuspid valve inserts lower (more apical) than the anterior leaflet of the mitral valve and the AV septum is that portion between the hinge points of the tricuspid and mitral valves. With AVC defects, the mitral valve (left AV valve) insertion is at the same level as the tricuspid valve (right AV valve). This displacement of the common hinge plane of the mitral valve towards the apex reduces the inlet-to-apex distance and increases the apex-to-outlet ventricular dimension, resulting in a "gooseneck" deformity of the left ventricular outflow tract with the potential to cause left ventricular outflow tract obstruction [69]. A *balanced* CAVC defect has appropriately sized left and right ventricles and the common AV valve is distributed equally over the ventricular masses. In an *unbalanced* CAVC *defect*, one ventricle is hypoplastic with the other ventricle receiving most of the AV valve tissue and ventricular blood flow because of *straddling* (insertion of chordae in the opposite ventricle) or *override* (insertion of chordae to the crest of the septum or the appropriate ventricle). AVC defects may be isolated or may appear as one element of a more complex lesion or syndrome. Approximately 40% of patients with trisomy 21 (Down syndrome) have AVC defects [66].

Ebstein anomaly is the most important cause of congenital tricuspid regurgitation and is thought to be due to abnormal delamination of the inlet zone of the right ventricle [70]. The septal and posterior leaflets do not attach to the annulus but are displaced downward toward the right ventricular apex. The portion of the right ventricle that extends from the true tricuspid annuls to the level where the septal and posterior leaflets attach is thin due to partial absence of myocardium and is termed the "atrialized" portion, whereas the trabecular and outlet portions make up the functional right ventricle. The anterior leaflet is large ("sail-like") and dysplastic and can obstruct the right ventricular outflow tract. Ebstein anomaly can be associated with abnormalities in left ventricular morphology, such as ventricular non-compaction and increased fibrosis of the wall and septum. Most patients with this anomaly have a PFO, and approximately 50% have an ASD [71]. Downward displacement of the leaflets is associated with discontinuity of the central fibrous body, thus producing a substrate for accessory AV connections and ventricular pre-excitation [70].

Tricuspid atresia is characterized by agenesis of the tricuspid valve and right ventricular hypoplasia. The region normally occupied by the tricuspid valve may be replaced by an atretic membrane, muscular tissue, or fibrofatty tissue, and an ASD is necessary for survival. With normally related great arteries, blood passes to the lungs through a VSD into a small right ventricle and pulmonary artery, whereas with transposition of the great arteries, blood reaches the lungs directly from the left ventricle. Isolated *tricuspid stenosis* is exceedingly rare.

Mitral valve stenosis is most commonly associated with other left-sided obstructive lesions, HLHS being at the most severe end of the spectrum and coarctation of the aorta, aortic arch hypoplasia, and subvalvular or valvular aortic stenosis in Shone's complex occurring with varying severity [72]. *Congenital mitral regurgitation* is more common than mitral stenosis and is usually associated with AVC defects.

Outflow tract septation and semilunar valve development

Cardiac neural crest cells are a subpopulation of the cranial neural crest and are crucial for normal cardiovascular development [29]. Cardiac neural crest cells contribute to the formation and remodeling of the aortic (pharyngeal) arch arteries, outflow tract septation, semilunar valvulogenesis, cap of the interventricular septum, parasympathetic innervation of the heart (neurons and supporting cells of cardiac ganglia), and cardiac conduction system [73, 74].

The outflow tract connects the primitive ventricle to the aortic arch arteries and is traditionally divided into three sections: the conus (proximal), the truncus (middle), and the aortic sac (distal) [75]. Septation of the outflow tract begins with the formation of a shelf of mesenchyme in the dorsal wall of the aortic sac in the area between the fourth and sixth pairs of aortic arch arteries [76]. This shelf, called the aorticopulmonary septum, elongates toward the truncus, thereby dividing the lumen of the aortic sac into the future intrapericardial portions of the aorta and pulmonary trunk. Cardiac neural crest cells delaminate from the cranial portion of the neural tube and migrate into pharyngeal arches 3, 4, and 6, and a subset of these cells migrates into the outflow tract (Figure 6.15). The outflow endocardial cushions are ridges of mesenchyme, formed by EMT of the underlying endocardium, that spiral into the outflow tract. Mesenchymal cells

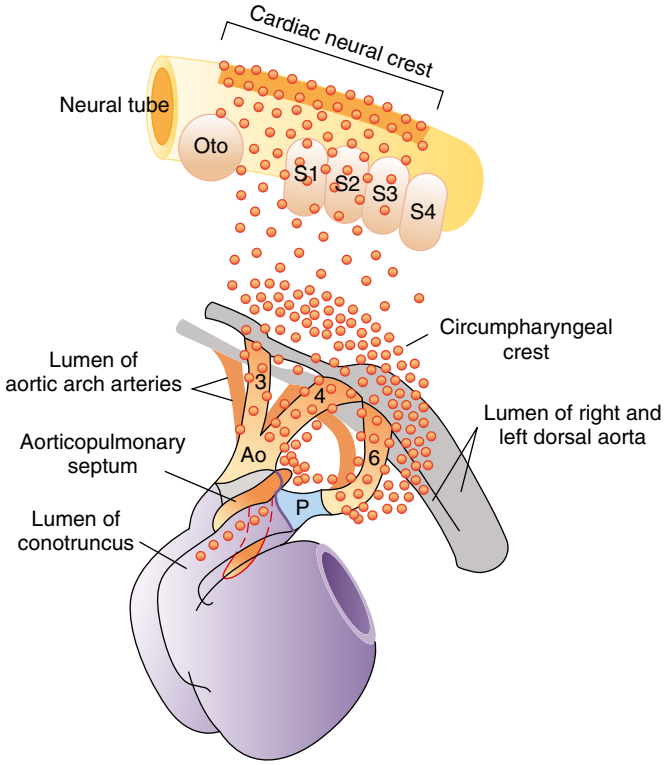


Figure 6.15 Cardiac neural crest. Migration of the cardiac neural crest to the circumpharyngeal ridge, caudal pharyngeal arches (3–6), and outflow tract depicted schematically. S1, S2, S3, S4, somites 1–4. Oto, otic vesicle; Ao, aorta; P, pulmonary artery. (Source: Kirby [23]. Reproduced with permission of Oxford University Press.)

from the pharynx, followed by neural crest cells, invade the truncal cushions to form two centrally placed columns, or prongs, in the shape of an upside-down "U" (Figure 6.16) [78]. These prongs will fuse with the aorticopulmonary septum distally and with the conal cushions proximally. Rotation of the developing pulmonary valve (see later in the chapter) is associated with spiraling of the aorticopulmonary septum and prongs, so that the developing aorta will connect with the rightward and cranial component of the aortic sac and the developing pulmonary trunk will connect with the leftward and caudal component of the aortic sac [79].

The convergence of the inflow and outflow poles during looping combined with the rotation and wedging processes brings the atria and outflow vessels into concordance with the AV valves and ventricles [75, 78]. In the conus, myocardial cells invade the cushions (myocardialization), which then bulge further into the lumen and subsequently meet and fuse in the midline. These conal cushions fuse most proximally with the AV cushion tissue and the crest of the muscular ventricular septum. Muscularization of the central conal cushion tissue and development of the adjacent aortic and pulmonary sinuses produce the *subpulmonary infundibulum* and a plane of space between the infundibulum and aortic root [79].

The developing pulmonary valve is initially posterior to and left of the developing aortic valve. Morphogenetic movement of the pulmonary valve (posterior to anterior, left of the aortic valve) brings it to its final position anterior and lateral to the aortic valve (Figure 6.9) [80]. This movement of the pulmonary valve is thought to be caused by the development of the subpulmonary conus (infundibulum), which also causes the pulmonary valve to be in a superior position relative to the aortic valve. Early in development, both the subpulmonary conus and the subaortic conus are situated above the right ventricle. Following torsion and a leftward shift of the outflow tract, resorption and shortening of the subaortic conus cause the aortic valve to sink inferiorly and posteriorly so that it comes to lie directly over the left ventricle and in fibrous continuity with the mitral valve (Figure 6.9) [81]. The conversion from the primitive, single in-series circulation to the double in-series circulation takes place during the fifth week of development.

Following outflow tract septation, the semilunar valves are formed as the mesenchyme in the outflow cushions is remodeled into the tri-leaflet aortic and pulmonary valves. Initially, three pairs of ridges, consisting of mesenchymal tissue covered by the endocardium, protrude into the lumen on each side of the divided truncus [78]. Valve sinuses are formed by excavation on the arterial (distal) face of the cusps. Thereafter, the leaflets are remodeled by mesenchymal apoptosis, blood flow, and shear stress to produce the delicate fibrous tissue seen in mature valves. Cells from the endocardium are the primary source of semilunar and AV valve fibroblasts, but fibroblasts derived from the epicardium also contribute to valve formation [76]. Cardiac neural crest cells are found at the tip of the leaflets and contribute to remodeling and maturation [74]. The role of cardiac neural crest in coronary vessel formation remains controversial.

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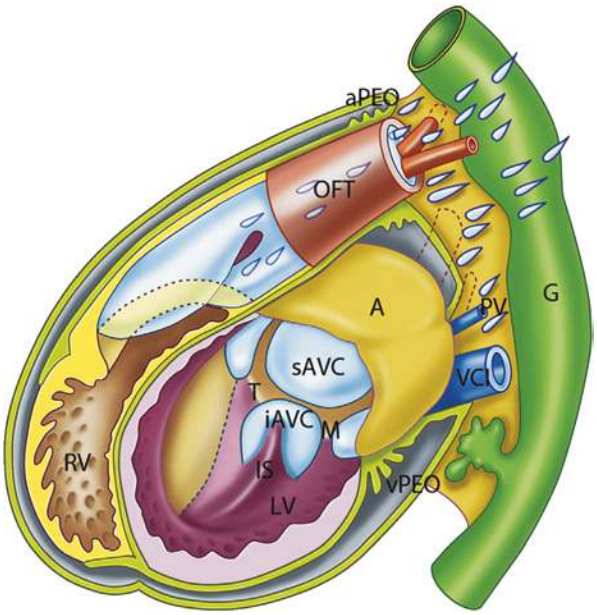


Figure 6.16 Schematic representation of the developing heart. Simplified model of a heart prior to ventricular septation. The roof of the atrium (A, light brown) is closed; therefore, atrial septation is not shown here. The anterior walls of the left ventricle (LV) and right ventricle (RV) are opened to reveal the inside. The interventricular foramen (primary foramen) is present. The inlet septum (IS) is connected to the inferior AV cushion (iAVC). The epicardium (olive green) covers most of the surface of the heart, but the venous proepicardial organ (vPEO; between liver and venous pole) and the arterial PEO (aPEO) surrounding the arterial pole are still present. The second heart field-derived part of the RV is shown in yellow, the endocardial cushions in light blue, neural crest cells in lavender, and the gut (G), including the liver, in green. AVC, atrioventricular canal; M, mitral ostium; OFT, outflow tract; PV, pulmonary vein; sAVC, superior AV cushion; T, tricuspid ostium; VCI, inferior cardinal vein. (Source: Gittenberger-de Groot et al. [77]. Reproduced with permission of Elsevier.)

Abnormalities of outflow tract septation

The loss or dysfunction of cardiac neural crest cells produces a wide spectrum of conotruncal and aortic arch abnormalities that are associated with syndromes linking defects in the heart with craniofacial and glandular (thyroid, parathyroid, and thymus) defects [74]. These include the 22q11 deletion syndromes, such as DiGeorge and velocardiofacial syndromes, CHARGE syndrome, fetal alcohol syndrome, retinoic acid embryopathy, Alagille syndrome, and Noonan and LEOPARD syndromes [75]. The association between thymus, thyroid and parathyroid abnormalities in these syndromes is explained by the fact that the neural crest cells contribute to the connective tissue of these three organs. Additionally, abnormalities of the SHF also produce outflow tract defects [78].

Persistent truncus arteriosus results from a failure in outflow tract septation (conotruncus and aorticopulmonary septum) combined with a virtual absence of the subpulmonary infundibulum and, thus, a VSD [69, 82]. Typically, the aortic and pulmonary valves are fused to form a single semilunar truncal valve. The origin of the pulmonary arteries from the truncal root varies and is dependent on the degree of the septation deficiency [83]. Incomplete outflow tract septation results in an *aortopulmonary window*. Aortoventricular tunnels are thought to result from abnormal excavation and maturation of the outflow cushions during the formation of the semilunar valves [79]. Unequal septation can result in either the aorta or pulmonary artery being *hypoplastic* relative to the other.

Tetralogy of Fallot is thought to result from underdevelopment of the subpulmonary infundibulum (conus) [84]. The smaller infundibulum causes anterior deviation of the conal septum and malalignment of the conal septum with the muscular ventricular septum, producing right ventricular outflow tract obstruction and a subaortic VSD [85]. The pulmonary valve is usually abnormal, and the reduced blood flow contributes, to some degree, to pulmonary artery hypoplasia. Some patients have *tetralogy of Fallot with pulmonary valve atresia (TOF/PA)* and varying degrees of hypoplasia of the main and branch pulmonary arteries.

Theories that have been proposed to explain TGA include resorption of the subpulmonary conus, causing the pulmonary valve to move inferiorly and posteriorly so that it comes to lie above the left ventricle and in fibrous continuity with the mitral and tricuspid valves [80], and failure of the aorticopulmonary septum to spiral [86]. Dextro- or D-TGA refers to TGA with normal looping of the heart to the right, whereas L-TGA refers to looping of the heart to the left. In D-TGA, there is AV concordance and VA discordance. *Congenitally or physiologically corrected TGA* is characterized by TGA and AV discordance (i.e. double discordance). In the more frequent form, referred to as L-transposition, there is levocardia with situs solitus of the atria and L-looping of the heart. The other form is a mirror image of the above with dextrocardia, inversion of the atria (situs inversus), and D-looping of the heart [87].

Persistence of both the subpulmonary and subaortic coni results in a *double outlet right ventricle*, whereas a deficiency of both results in a *double outlet left ventricle* (very rare); in either case, there is almost always a VSD.

Fused or absent pulmonary commissures produce *pulmonary valve stenosis*, in which the valve is typically mobile and dome-shaped with a small and sometimes eccentric orifice [88]. *Critical pulmonary stenosis* is a severe form of pulmonary stenosis in the neonate that is considered a ductal-dependent lesion because a *patent ductus arteriosus* (PDA) is essential for pulmonary blood flow.

Obstruction of the left ventricular outflow tract may occur at the valvular, subvalvular, or supravalvular levels. The most common aortic valve anomaly is a *bicuspid aortic valve* [2]. This malformation is also thought to be the most common cardiac defect (occurring in 1–2% of the population). It may be an incidental finding or may result in a clinical presentation in childhood or adult life, and it can occur in isolation or in association with left-sided obstructive lesions [89]. There are several variants, the most frequent being characterized by commissural fusion (most commonly between the coronary cusps), creating a functionally bicuspid structure, and the far less frequent "true" bicuspid valve. *Critical aortic valve stenosis* in the neonate is a ductal-dependent lesion in that a PDA is necessary for systemic perfusion. The valve is usually unicommisural or bicommisural and incompletely differentiated with thickened, redundant, and rolled cusps and leaflets consisting of immature loose connective tissue (myxomatous) [90]. Dysplastic valves, rather than commissural fusion, obstruct the orifice. Severe aortic stenosis or *aortic atresia* can be part of a spectrum of left-sided obstructive lesions associated

with hypoplasia of the left ventricle, ascending aorta and/or arch, mitral valve stenosis or atresia, and endocardial fibroelastosis of the left ventricle (i.e. HLHS) [64].

Subvalvular aortic stenosis has a number of embryologic etiologies. Malalignment of the conal septum with the muscular interventricular septum results in posterior projection of the conal septum into the left ventricular outflow tract and an associated VSD. This pathology may be seen within the context of an interrupted aortic arch. *Familial hypertrophic cardiomyopathy* is an autosomal dominant developmental abnormality most commonly due to mutations in the contractile protein (sarcomere) genes, but it may also be due to mutations in non-sarcomeric genes that are associated with mitochondrial defects, potassium channel abnormalities, and abnormalities of protein kinase A [91]. A *discrete fibromuscular ridge* or *membrane* below the aortic valve can also cause subaortic stenosis.

Congenital supravalvular aortic stenosis (SVAS) is caused by the deletion of or a loss-of-function mutation in the elastin gene on chromosome 7q11.23. In the majority of cases, SVAS occurs in association with Williams–Beuren syndrome, which is frequently referred to as Williams syndrome (WS) [92, 93]. In other cases, SVAS is inherited as an autosomal dominant disorder or results from sporadic mutations and occurs without mental retardation, elfin facies, distinctive behavioral traits, and neonatal hypocalcemia associated with WS [94]. During the early stages of development, the smooth muscle cells from patients with WS and non-syndromic SVAS express only about 15 and 50%, respectively, of the normal levels of the elastin-precursor tropoelastin [95]. The resultant arterial media has a reduced elastin content, pathologic alignment of the elastin fibers, an increased collagen content, and an increased number of hypertrophied smooth muscle cells. The entire ascending aorta may be narrowed (aortopathy) in about 30% of patients, and up to 80% of patients will have peripheral pulmonary artery stenosis [96].

Heritability and genetic etiologies of non-syndromic left-sided obstructive lesions are highly heritable. First-degree relatives of an individual with a left-sided obstructive lesion have a 20% chance of having CHD (most often a bicuspid aortic valve) [97]. The genetic causes of left-sided obstructive lesions overlap due to genetic heterogeneity (Table 6.1, Figure 6.17) and help explain the phenotypic variability within families with the same genetic variant [98–100].

Table 6.1 Genes associated with left-sided obstructive lesions based on CHD type

Associated gene	Aortic valve		Left ventricle : HLHS	Aorta : CoA & IAA
	AS	BAV		
ELN	X	X		
GATA4/GATA6		X		
ROBO4		X		
SMAD6	X	X		X
TAB2		X		
NKX2-5	X	X	X	X
NOTCH1	X	X	X	X
GJA1			X	
HAND1			X	
ZIC3			X	
MCTP2			X	X
MYH6	X		X	X
NR2F2	X		X	X
CFC1				X
FOXC1				X
HEY2				X
LEFTY2				X
MATR3				X
NFATC1				X
TBL1Y				X
TBX1				X
TRPM2				X
VEGF				X

AS, aortic stenosis; BAV, bicuspid aortic valve; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch.
Source: Parker [98]. Reproduced with permission of John Wiley & Sons.

KEY POINTS: CARDIAC SEPTATION

- Cardiac septation begins after the looping stage with the eventual creation of four chambers and two distinct circulations.
- The process of cardiac septation involves the muscular septa in the atrial and ventricular chambers, the AV and outflow tract endocardial cushions, and the dorsal mesenchymal protrusion.
- Abnormalities in this process can result in septation defects at the atrial and/or ventricular levels, altered AV valve development, abnormalities of outflow tract septation, and semilunar valve pathology.

Epicardium and coronary artery development

After looping of the linear heart tube, the epicardium covers the heart as well as the intrapericardial portion and roots of the great arteries. The epicardium develops from the proepicardial organ (PEO) comprising medusa-like villi that arise from the *splanchnic mesoderm of the ventral pharynx* (Figure 6.16) [26, 30]. The venous PEO (vPEO) is derived from mesenchyme near or in the liver and begins as protrusions of splanchnic mesoderm at the venous pole at the back of the pericardial cavity. The vPEO gives rise to the epicardium that will cover the atria, AVC, and ventricles. Likewise, the splanchnic mesoderm of the ventral pharynx at the arterial pole, which is analogous to the vPEO, gives rise to the arterial PEO (aPEO) that will cover the outflow tract with the epicardium. Gittenberger-de Groot has shown that after the epicardium has invested the myocardium, a subset of cells undergoes EMT and migrates into the subepicardial space [101]. These epicardially derived cells (EPDCs) invade the myocardium and differentiate into fibroblasts, vascular (coronary) smooth muscle cells, endothelial cells, hematopoietic cells, fat cells, and pericytes [102]. The epicardially derived fibroblasts become the interstitial fibroblasts, the annulus fibrosus, and the adventitial coronary fibroblasts. The epicardium is necessary for myocardial growth, and interstitial fibroblasts are crucial to the formation of the thick compact myocardium.

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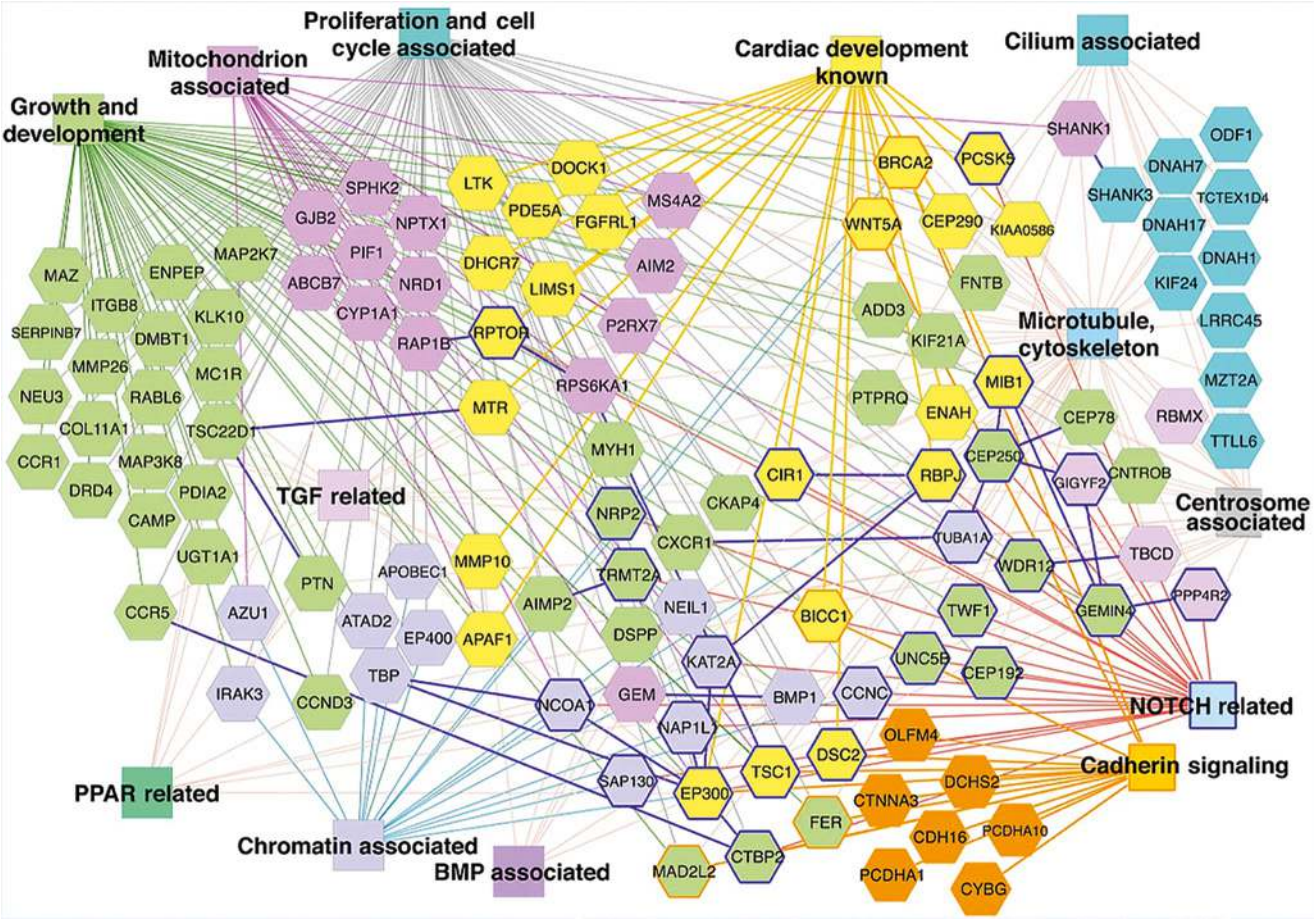


Figure 6.17 Mutations recovered from HLHS patients. ToppCluster-generated interactome network of multi-hit genes recovered from subjects with HLHS and HLHS mutant mice. Genes (hexagons) associated with heart development and various gene ontology biological processes (color rectangles) are shown with corresponding color. Dark blue-outlined hexagons are NOTCH-related genes. Protein-protein interactions are indicated as solid dark blue lines between genes. (Source: Yagi et al. [99]. Reproduced with permission of Springer Nature.).

Nutrient delivery to the myocardium occurs in three sequential and overlapping phases. Although the early myocardium is avascular, the inner trabecular zone of the myocardial wall has venous sinusoids (trabecular channels) lined by the endocardium through which nutrients diffuse. With the formation of the epicardium after cardiac looping, a subepicardial endothelial plexus forms from the EPDCs and undergoes vasculogenesis, angiogenesis, and arteriogenesis [103]. Arteriogenesis is the coating of the initial coronary plexus by smooth muscle cells and pericytes. The coronary plexus penetrates the myocardium, and some of the channels will communicate with the intratrabecular venous sinusoids. The density of the coronary plexus is not uniform across the myocardial wall, being higher on the outer epicardial side than on the inner endocardial side [104]. The subepicardial vascular network later undergoes remodeling to produce the coronary arteries and veins with adult branching characteristics. As reported by Waldo et al. [103] and Smart et al. [105], the final step in the development of the coronary circulation is ingrowth of the peritruncal coronary capillary plexus into the base of the aorta (Figure 6.18). Multiple small vessels penetrate each aortic sinus. In the right and left aortic sinuses the multiple channels coalesce to form the main stems of the right and left coronary arteries, whereas the channels in the remaining (non-coronary) sinus regress.

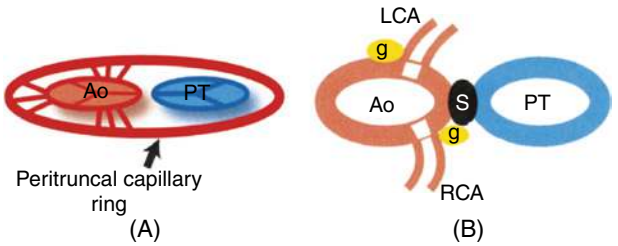


Figure 6.18 Left (LCA) and right (RCA) coronary artery development. (A) Multiple channels penetrate the aortic (Ao) wall in all of the aortic sinuses from the peritruncal ring. (B) Only the ones in the right and left sinuses survive and coalesce to form the main stems of the LCA and RCA. PT, pulmonary trunk; g, cardiac ganglia; S, aorticopulmonary septum. (Source: Waldo et al. [103]. Reproduced with permission of John Wiley & Sons.)

Abnormalities of epicardial development

Normal development of the compact myocardium requires a trophic interaction between the cardiomyocytes and

EPDCs [30]. Abnormal EPDC function results in *ventricular non-compaction*, a cardiomyopathy characterized by a spongy myocardium, and has a predilection for the left ventricle.

Coronary artery fistulae may arise from either the right or left coronary artery and most frequently terminate in the right heart [106]. Fistulae can occur in isolation or in association with other lesions. In some cases of pulmonary atresia with an intact ventricular septum (PA/IVS) and in some forms of HLHS [107], a significant portion of the ventricle may be dependent on blood supply from the hypertensive right (PA/IVS) or left ventricle, respectively. Flow into a lower pressure chamber produces myocardial ischemia by a coronary steal and ventricular volume overload.

Vascular channels from the peritruncal ring normally penetrate the aortic sinuses. However, penetration of the pulmonary artery results in an *anomalous origin of the coronary artery from the pulmonary artery*, the most common form being the left coronary artery from the pulmonary artery (ALCAPA) [108, 109]. Coronary steal can occur, in which the blood flow is reversed into the pulmonary artery due to the lower vascular resistance of the pulmonary circulation and/or the higher pressure of collateral circulation from the normal coronary artery. Also, blood flowing antegrade through the anomalous coronary artery has a lower oxygen content than normal.

Congenital atresia of the left coronary artery and *anomalous aortic origin of the left or right coronary artery from the right or left coronary sinus*, respectively, are generally rare but have been associated with sudden death [108, 109].

KEY POINTS: EPICARDIUM AND CORONARY ARTERY DEVELOPMENT

- The epicardium is derived from the proepicardial organ which comprises villi that arise from the splanchnic mesoderm of the ventral pharynx at the venous and arterial poles.
- Epicardially derived cells undergo differentiation into fibroblasts, coronary smooth muscle cells, and endothelial and hematopoietic cells.
- The development of the coronary circulation involves various steps, the last one consisting of ingrowth of the peritruncal coronary capillary plexus into the base of the aorta.
- Abnormal epicardial development can result in certain types of cardiomyopathies and anomalies that involve the coronary arteries.

Development of the conduction system

The myocardium of the primitive heart tube has no morphologically distinct conducting cells [110]. The primitive pacemaker (i.e. area with the cells with the fastest intrinsic rate) is located at the junction of the sinus venosus and the primitive atrium. Before the AV and semilunar valves develop, a unidirectional, slowly transmitted, depolarizing impulse (represented by a sinusoidal electrocardiogram) generates a mechanical contraction wave that pushes blood from the venous pole to the arterial pole [34].

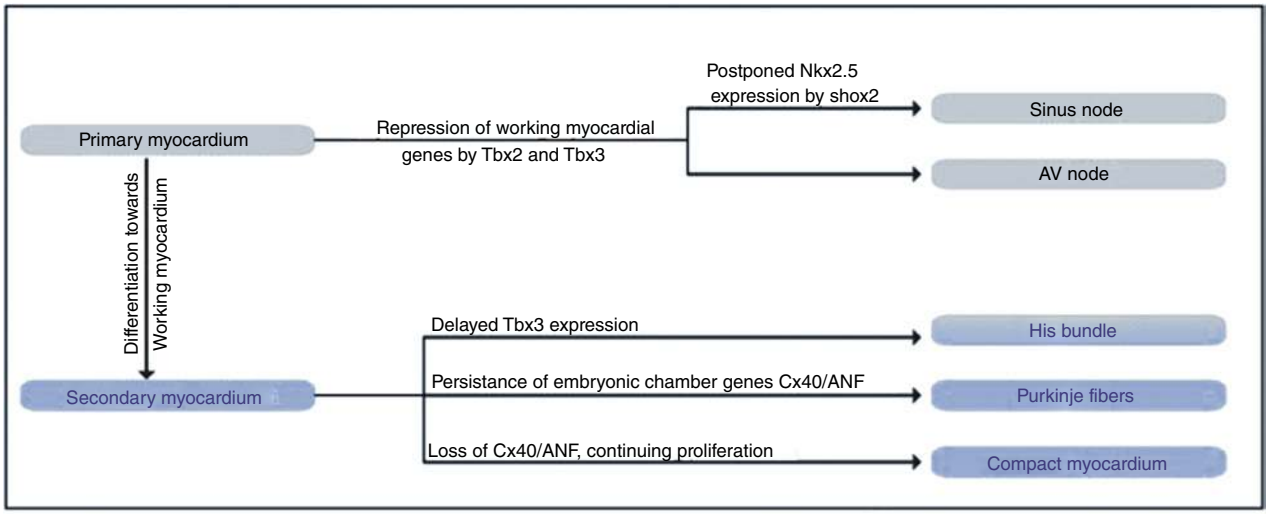
With elongation of the heart tube, the myocardial cells of the developing ventricular and atrial chambers differentiate into a *working* (contractile) myocardial phenotype characterized by fast-conducting gap junctions and sarcomere components [111]. Myocardial cells at the venous pole, AVC, and outflow tract differentiate into specialized *conductive* myocardium. Although these cells have elements of working myocardium (including contraction, autorhythmicity, intercellular conduction, and electromechanical coupling), they retain their primary phenotype of sparse gap junctions and slow conduction (Figure 6.19). The cardiomyocytes of the conduction system necessary for the generation and propagation of the electrical impulses for coordinated contraction comprise ~2% of the myocardial mass [112]. With the differentiation of myocytes into working and conductive myocardium, the electrocardiogram resembles that of the formed heart [113].

The *sinoatrial node* (SAN) is detectable at approximately 32 days of gestation. It develops from myocardial cells located at the junction of the right common cardinal vein (which drains into the right horn of the sinus venosus) and the right atrium, ultimately becoming "comma-shaped" with its head at the junction of the SVC and the right atrium and its tail incorporated into the crista terminalis [114]. Normal development of the cardiac conduction system is transcription factor-dependent. TBX3 is expressed in the sinoatrial node and its deletion leads to abnormalities including VSD, Wolff-Parkinson-White arrhythmia, and sinus node dysfunction. It is both a positive regulator of the development of the normal atrioventricular conduction system and a negative regulator of abnormal accessory atrioventricular pathways [115]. Unlike other areas of myocardial development, normal sinus myocardium development (and thus normal sinus node development) depends upon the *absence* of NKX2.5 expression due to suppression by SHOX2. The sinus myocardium is derived from TBX18-positive cells, and the sinus node develops hypoplastically in its absence. Thus, a complex interplay between TBX18, SHOX2, and NKX2.5 is required for normal sinus myocardium and sinus node development [26]. Nodal cells in the left cardinal vein regress to become the ligament of Marshall [110]. It has been established that specific conduction pathways through the atrial myocardium do not exist [116, 117].

The *AV node* (AVN) is detectable at approximately 33 days of gestation. It develops from slow-conducting myocardium within the dorsal AVC. The AVN becomes located in the triangle of Koch, and the cells of the AVN are in direct continuity with the atrial and ventricular myocardium. The AVN retains its primary phenotype of slow conduction so that there is an appropriate AV delay. The development of AV node progenitor cells is dependent upon NKX2.5 transcription factor binding. Pathogenic variants that significantly alter the binding result in AV block, with or without CHD [25].

The *AV (His) bundle, left and right bundle branches* and *Purkinje fibers* develop from fast-conducting ventricular myocardium; the AV bundle from cells in the crest of the interventricular septum, and the bundle branches and Purkinje network from subendocardial myocytes along the ventricular septum [111].

An important step in the development of the conduction system is establishing electrical discontinuity between the atrial and ventricular myocardium at the AV junction.

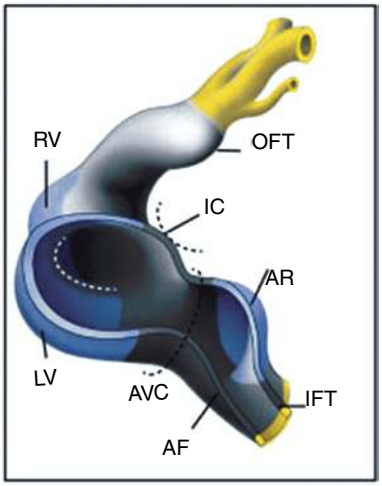


(A)

	Primary	Nodal	His bundle	Purkinje	Compact
Automaticity	High	High	High	Low	Low
Conduction velocity	Low	Low	High	High	High
Contractility	Low	Low	Low	Low	High

	IFT	AR	AF	AVC	IC	LV	RV	OFT
Tbx1	–	–	–	–	–	–	–	+
Tbx2	+	–	+	+	+	–	–	+
Tbx3	–	–	+	+	+	–	–	–
Tbx5	+	+	+	+	+	+	–	–
Tbx18	+	–	–	–	–	–	–	–
Tbx20	+	+	+	+	+	+	+	+

(B)



(C)

Figure 6.19 Differentiation of the primary myocardium. (A) Flow chart of the differentiation of primary and secondary myocardium into the different kinds of adult-type myocardium. (B, upper table) Characteristics of different kinds of myocardium in terms of their contraction and electrophysiological behavior. (B, lower table) Summary of the expression pattern of different T-box transcription factors in different parts of the heart. Note that the primary myocardium always expresses either Tbx2, Tbx3, or both. (C) Schematic of the chamber-forming (ballooning) heart (gray, primary myocardium; blue, secondary myocardium). The gray area at the top of ventricular septum (white dotted line) retains characteristics of the primary myocardium and will become the atrioventricular bundle. AF, atrial floor; AR, atrial roof; AVC, atrioventricular canal; IC, inner curvature; IFT, inflow tract; LV, left ventricle; OFT, outflow tract; RV, right ventricle. (Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.)

Epicardial cell-derived fibroblasts in the AV groove invade the AV myocardium inferior to the AVN and make contact with the endocardial cushion mesenchyme to form the *annulus fibrosus*, or crux of the heart. Because the annulus fibrosus insulates the atria from the ventricles, the AV conduction system provides the only myocardial continuity between the atria and ventricles. The complex genetics, transcription factors, and signaling pathways of cardiac conduction system development and function have recently been reviewed [112, 118].

Abnormalities of conduction system development

Normal development of the conduction system is dependent upon a concordance of the atrial and ventricular chambers, correct alignment of the atrial and ventricular septa, and complete closure of the ventricular septum [119]. Thus, from an embryologic perspective, abnormalities of the conduction system would be expected in lesions that involve AV concordance, the AVC, single ventricles, atrial isomerism, or combinations thereof [120, 121].

Congenitally corrected TGA (CCTGA) with L-loop ventricles is associated with displacement of the AVN within the right atrium to an anterior and lateral position beneath the opening of the right atrial appendage [122]. The AV bundle is longer than normal and passes across the anterior surface of the subpulmonary outflow tract to reach the morphologic right ventricle. Infants may be born with complete AV block, but for those born without block, the risk of natural onset

complete AV block increases by 2%/year [123]. In *CCTGA with D-loop ventricles and atrial situs inversus*, the AVN is typically in a left-sided triangle of Koch.

In *AVC defects*, the AVN is displaced posteriorly and inferiorly to lie low in the atrial septum and anterior to the coronary sinus ostium. The AV bundle is displaced posteriorly, is elongated, and courses along the lower rim of the VSD; this gives rise to the superior (left) QRS axis seen on an electrocardiogram [124]. With *perimembranous VSDs*, the AV bundle can be longer and is typically located along the postero-inferior rim of the defect. In *single ventricle* abnormalities, the locations of the AVN and AV bundle can vary widely.

Accessory pathways are accessory bundles of cardiomyocytes that electrically connect the atria and ventricles, providing the substrate for some supraventricular arrhythmias (as occurs in Wolff–Parkinson–White syndrome and Mahaim tachycardia) [124]. Right-sided pathways and some left-sided pathways run subendocardially. The most common right atrial locations in children are the left free wall and the posteroseptal right free wall [119]. Ebstein anomaly is frequently associated with Wolff–Parkinson–White syndrome and other accessory pathways.

Atrial conduction disturbances and arrhythmias are frequently related to sinus venosus myocardium and thus they tend to take place at particular anatomic sites, such as the crista terminalis, ostia of the caval veins, coronary sinus, pulmonary veins, and the ligament of Marshall [124]. The structure of the AVN is complex, both anatomically and electrophysiologically, and in many normal hearts, it provides the substrate (two pathways with different electrophysiological characteristics) for dual AVN physiology and *AV nodal re-entry tachycardia* (AVNRT).

Gene mutations that affect ion channels give rise to *cardiac channelopathies*; the most important of these are long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome [125, 126].

KEY POINTS: DEVELOPMENT OF THE CONDUCTION SYSTEM

- The primitive pacemaker is located at the junction of the sinus venosus and the primitive atrium.
- The AV node retains its primary phenotype of slow conduction allowing for appropriate AV delay, whereas the AV bundle, left and right bundle branches and Purkinje fibers develop from fast-conducting ventricular myocardium.
- Abnormalities of the conduction system are expected in lesions that alter the AV concordance, proper alignment of the atrial and ventricular septa, and complete closure of the ventricular septum.

Development of the aortic arches

Blood vessels are formed by the aggregation of angioblasts (splanchnic mesoderm that has differentiated into endothelial cell precursors) into small endothelial-lined channels that connect to form vascular networks (vasculogenesis), which grow through the sprouting and branching of vessels (angiogenesis). Depending on the site of the vascular network, cells from the mesoderm, neural crest, or epicardium associate with the endothelial cells to form vascular smooth muscle, thereby stabilizing the vessel wall [127]. The dorsal aortae are bilateral, parallel, longitudinal channels that form in the mesoderm on either side of the notochord, adjacent to the ventral pharyngeal endoderm. The aortic sac is connected to the paired dorsal aortae by the artery of each pharyngeal arch; these vessels are referred to as pharyngeal arch arteries (PAAs) or aortic arch arteries [9]. Pioneering work by Kirby, and later by Poelmann and Gittenberger-de Groot, demonstrated that cardiac neural crest cells migrate into the mesoderm of the pharyngeal arches (3, 4, and 6) and surround the endothelial cells to form the smooth muscle of the PAAs [29, 128–130]. The PAAs are not all present simultaneously but form over time in a symmetric pattern cranially to caudally. The neural crest cells are critical for remodeling, whereby some segments of the aortic arch apparatus and dorsal aortae regress, while other segments transform and persist to produce the mature asymmetric pattern (Figure 6.20).

The dorsal aortae fuse in a caudal-to-cranial direction up to the seventh somite. The seventh somite is supplied by the seventh intersegmental artery, which forms the left subclavian artery and contributes to the formation of the right subclavian artery. The dorsal aortae give off dorsal intersegmental arteries, which supply the spinal cord and developing somites [132]. Longitudinal anastomoses form between the intersegmental arteries, with those from the first to the seventh forming the vertebral artery. The first six intersegmental arteries regress after the vertebral artery is formed, and the vertebral artery arises from the seventh intersegmental artery, which itself forms part of the subclavian artery.

Abnormalities of aortic arch development

Abnormalities of the aortic arch occur when segments of the fourth aortic arch fail to regress or regression occurs at an abnormal site; this can be explained by Edwards' hypothetical double aortic arch model (Figure 6.21) [134]. The aortic arch is referred to as left- or right-sided to indicate which mainstem bronchus the arch crosses over. Congenital variants and aortic arch anomalies have been reviewed by Hanneman and colleagues [135]. The normal left aortic arch (LAA) results from regression of the segment of the right arch between the right subclavian artery and the descending aorta. Conversely, a *right aortic arch* (RAA) with mirror-image branching is produced when the LAA regresses between the left subclavian artery and the descending aorta. An RAA with mirror-image branching is frequently associated with cardiac malformations. A *double aortic arch* results from the persistence of both fourth aortic arches. Regression of the segment between the right carotid and right subclavian arteries results in an LAA with an *aberrant right subclavian artery*, whereas regression of the segment between the left carotid and left subclavian arteries results in an RAA with an *aberrant left subclavian artery*. An *interrupted aortic arch* (IAA) results from the regression of both the right and left fourth aortic arches. The most common type of IAA is type B, in which there is an interruption between the left carotid and left subclavian arteries and normal regression of

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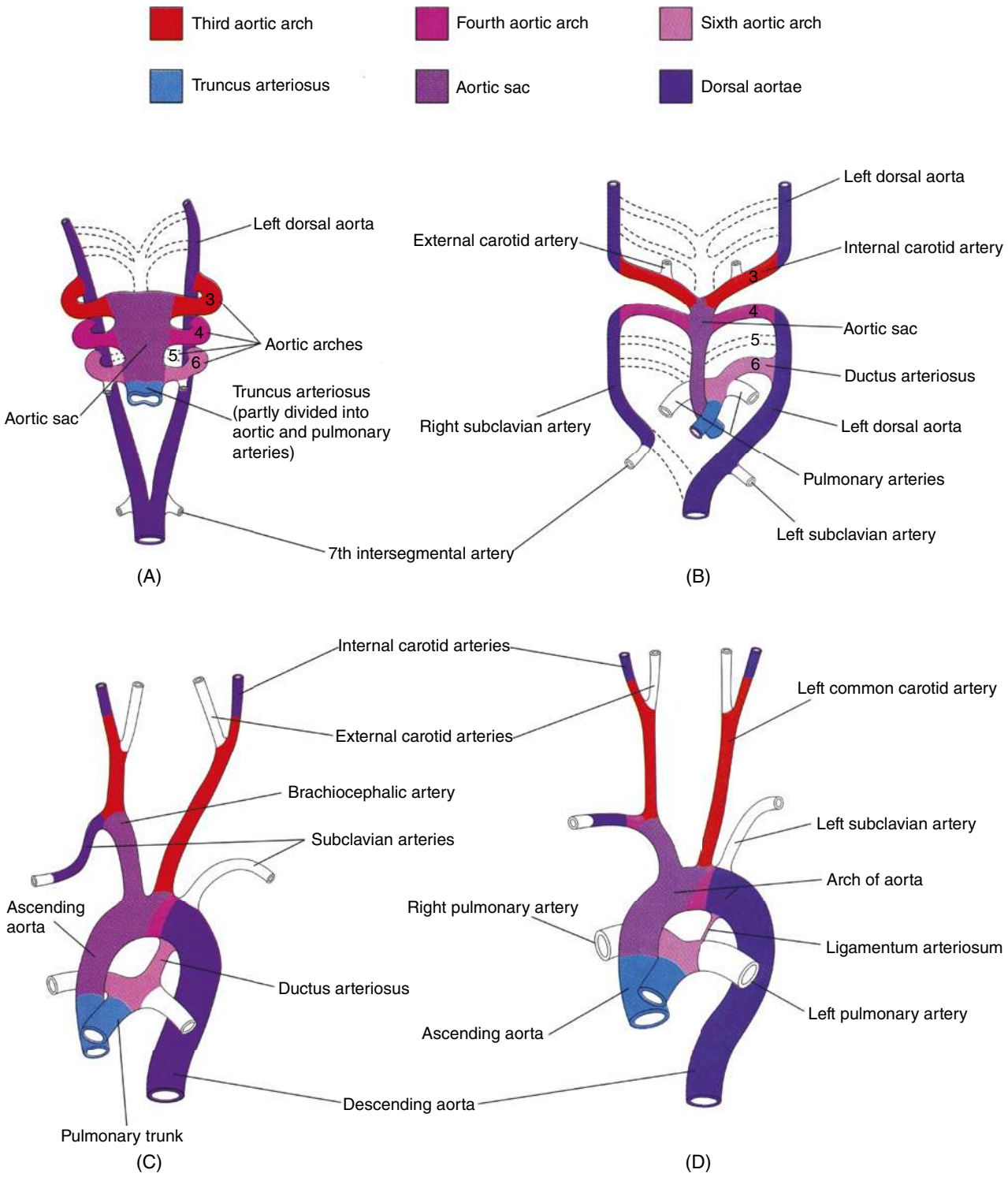


Figure 6.20 Schematic drawings illustrating the arterial changes that result during the transformation of the truncus arteriosus, aortic sac, pharyngeal arch arteries, and dorsal aortae into the adult arterial pattern. The vessels that are not colored are not derived from these structures. (A) Pharyngeal arch arteries at 6 weeks; by this stage, the first two pairs of arteries have largely disappeared. (B) Pharyngeal arch arteries at 7 weeks; the parts of the dorsal aortae and pharyngeal arch arteries that normally disappear are indicated with ***broken lines***. (C) Arterial arrangement at 8 weeks. (D) Sketch of the arterial vessels of a 6-month-old infant. Note that the ascending aorta and pulmonary arteries are considerably smaller in (C) than in (D). This represents the relative flow through these vessels at the different stages of development. Observe the large size of the ductus arteriosus in (C) and that it is essentially a direct continuation of the pulmonary trunk. The ductus arteriosus normally becomes functionally closed within the first few days after birth. Eventually, the ductus arteriosus becomes the ligamentum arteriosum, as shown in (D). (Source: Moore et al. [131]. Reproduced with permission of Elsevier.)

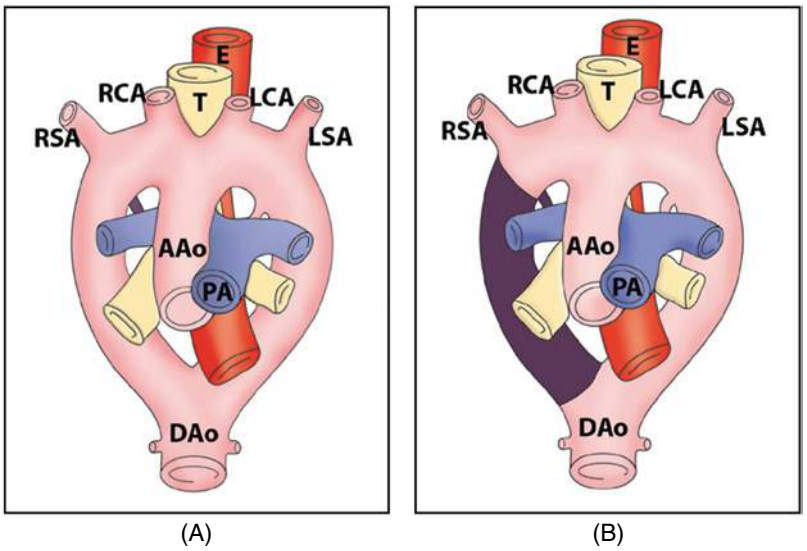


Figure 6.21 Diagram of Edward's developmental model of the aortic arch. (A) Hypothetical double aortic arch system in which there is an aortic arch and ductus arteriosus on each side encircling the trachea (T) and esophagus (E), with the carotid and subclavian arteries arising bilaterally from the respective arches. The descending aorta is in the midline. (B) Normal arch branching results from interruption of the dorsal segment of the right arch between the right subclavian artery and descending aorta with regression of the right ductus arteriosus. AAo, ascending aorta; DAo, descending aorta; LCA, left carotid artery; LSA, left subclavian artery; PA, pulmonary artery; RCA, right carotid artery; RSA, right subclavian artery. (Source: Turkvatan et al. [133]. Reproduced with permission of The Korean Radiological Society.)

the right aortic arch. It is estimated that 50% of cases of IAA type B are due to 22q11.2 deletion syndrome [136]. Smooth muscle differentiation in the outflow tract is dependent upon the histone deacetylase *Hdac3* and its loss in the neural crest of mouse models leads to IAA [137]. A *vascular ring* is an aortic arch anomaly in which the trachea and esophagus are completely encircled by vascular structures, which may be patent or consist of fibrous remnants, such as the ligamentum arteriosum. When the trachea and esophagus are not completely encircled, the abnormality is referred to as a *vascular sling*. Aortic arch anomalies can be associated with tracheobronchial and/or esophageal compression and, in the case of a pulmonary artery sling, malformations of the trachea [138].

Coarctation of the aorta is a focal narrowing of the aorta, usually consisting of a discrete posterior shelf or ridge caused by infolding or thickening of the aortic media with the inner part of the ridge composed of ductal tissue [139]. The site of the coarctation may be preductal, juxta- or paraductal, or postductal. It is most commonly preductal in infants, both pre- and paraductal in young children, and postductal beyond about 15 years of age. The histological architecture does not vary with the location. Coarctation is thought to be due to ductal tissue extending into the wall of the aorta (ductus tissue theory) and an abnormal flow pattern due to lesions resulting in decreased flow into the ascending aorta (hemodynamic theory) [140]. Thus, it is frequently associated with a bicuspid aortic valve, aortic stenosis, hypoplasia of the aortic arch, small left-sided structures, and VSDs.

PDA is an open ductus arteriosus beyond the first three postnatal days, with the incidence being inversely proportional to gestational age at birth [141]. In a preterm infant, a PDA is thought to be due to immaturity of the smooth muscle and oxygen sensing mechanisms. An *isolated PDA* in a full-term infant is most likely a congenital malformation of the vessel wall with different histologic features and a genetic origin [142]. The molecular mechanisms underlying ductal closure and remodeling have recently been reviewed [143]. A PDA may occur in isolation, particularly with prematurity, or in association with almost any other congenital cardiac anomaly. It is lifesaving in some forms of CHD.

KEY POINTS: DEVELOPMENT OF THE AORTIC ARCHES

- During development, the initial arterial pattern becomes modified, and some vessels regress completely, allowing for a transformation into the definitive vascular pattern.
- Neural crest cells are critical for the development of the aortic arches.
- Abnormalities of the aortic arch occur when segments of the fourth aortic arch fail to regress or regression occurs at an abnormal site.

Development of the pulmonary and systemic veins

Pulmonary veins

The lungs and tracheobronchial tree develop from the respiratory diverticulum, a ventral outgrowth from the foregut. Early in development, the lungs have the same venous

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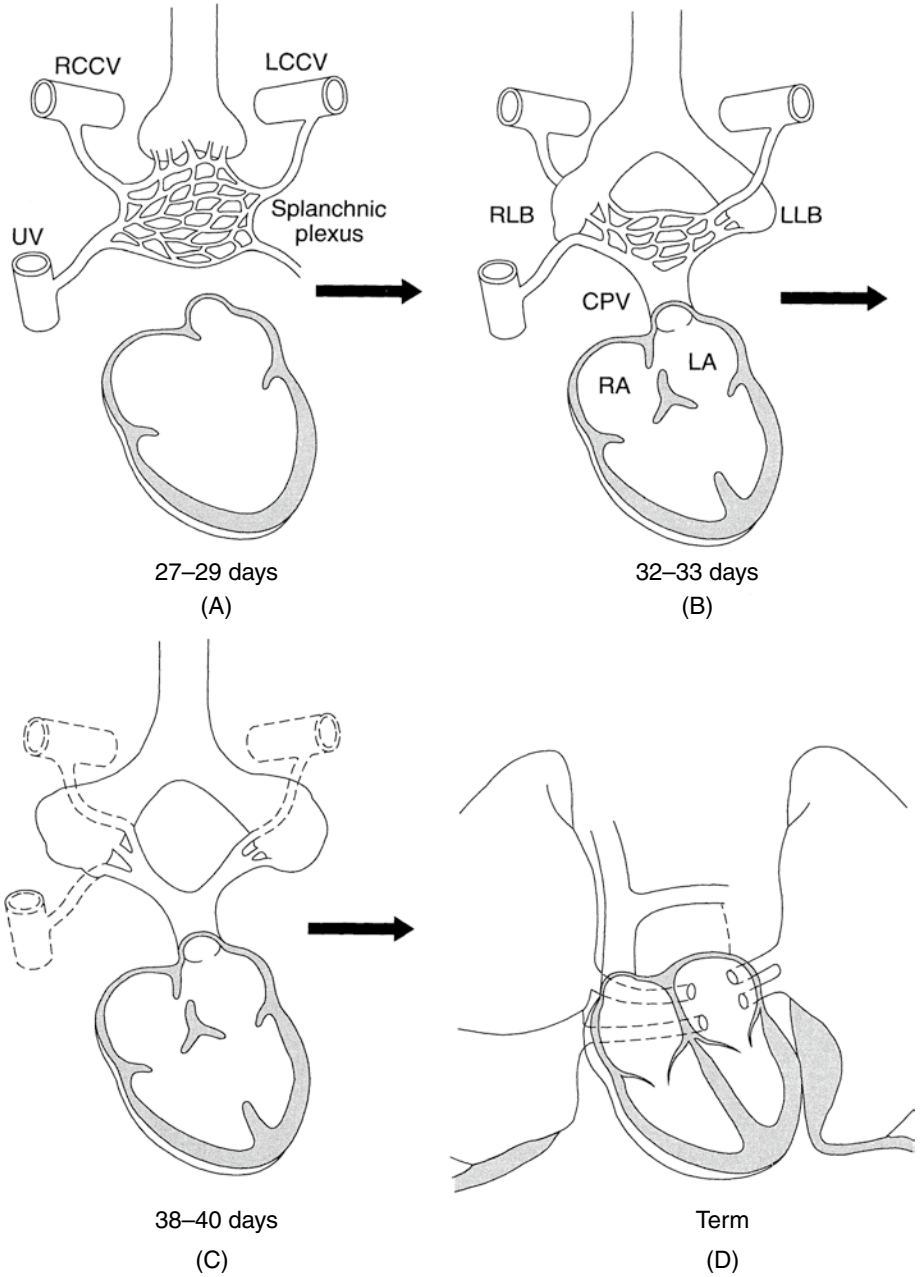


Figure 6.22 Development of the pulmonary veins. (A) At 27–29 days of gestation, the primordial lung buds are enmeshed by the vascular plexus of the foregut (splanchnic plexus). No direct connection to the heart is present at this stage. Instead, multiple connections are present to the umbilicovitelline and cardinal venous systems. A small evagination can be seen in the posterior wall of the left atrium to the left of the developing septum secundum. (B) By the end of the first month of gestation, the common pulmonary vein establishes a connection between the pulmonary venous plexus and the sinoatrial portion of the heart. At this time, the connections between the pulmonary venous plexus and the splanchnic venous plexus are still patent. (C) Subsequently, the connections between the pulmonary venous plexus and the splanchnic venous plexus involute. (D) The common pulmonary vein (CPV) incorporates into the left atrium so that the individual pulmonary veins connect separately and directly to the left atrium. LA, left atrium; LCCV, left common cardinal vein; LLB, left lung bud; RA, right atrium; RCCV, right common cardinal vein; RLB, right lung bud; UV, umbilical vein. (Source: Brown et al. [144]. Reproduced with permission of Wolters Kluwer.)

drainage as the foregut, via the splanchnic plexus into the cardinal and umbilicovitelline (systemic) veins (Figure 6.22).

The primary pulmonary vein develops by canalization within the dorsal mesocardium to form a channel [50]. Endothelial invagination from the left side of the primitive atrium into the dorsal mesocardium delineates the future orifice of the primary pulmonary vein [49]. This invagination is surrounded by ridges of the dorsal mesocardium, forming a pit (pulmonary pit) cephalad to the junction of the left and right horns of the sinus venosus and to the left

of the developing septum primum. Further canalization of the primary pulmonary vein brings it into continuity with the cavity of the developing left atrium, and by the end of the first month of gestation, the primary pulmonary vein has established a connection between the pulmonary venous plexus of the lung bud and the sinoatrial portion of the heart. Once a connection has been established between the primary pulmonary vein and the left atrium, the pulmonary venous plexus loses its connections with the systemic veins. Then, the common pulmonary vein incorporates into the left atrium so that the individual pulmonary veins connect separately and directly to the left atrium. At the connection of the developing pulmonary vein and atrium, pulmonary mesenchymal cells differentiate into pulmonary myocardial cells that form a sleeve of myocardium around the developing pulmonary vein. PITX2c is crucial in the differentiation of the pulmonary vein myocardium. Pitx2c-deficient mice fail to form primary pulmonary myocardial cells and thus the pulmonary myocardial sleeve [145].

Abnormalities of pulmonary vein development

Total anomalous pulmonary venous connection (TAPVC) results from a failure to establish the normal connection between the common pulmonary vein and the pulmonary venous plexus before the connections with the splanchnic venous system regress. All the pulmonary veins join a common horizontal or vertical vein behind the left atrium, which can drain via the supracardiac, cardiac, or infracardiac (infradiaphragmatic) route into the right heart circulation, producing a left-to-right shunt. Atresia of only the right or left portions of the common pulmonary vein before the connections with the splanchnic venous system regress results in *partial anomalous pulmonary venous connection* (PAPVC) with drainage into derivatives of the left or right cardinal systems. Both TAPVC and PAPVC produce a left-to-right shunt and can be associated with pulmonary venous obstruction. Pulmonary veins can also be *hypoplastic* or *atretic*, with the most common variation in the number of pulmonary veins being a *single pulmonary vein* on either the right or left side (prevalence of about 24% in anatomic studies) [146]. *Cor triatriatum* is an oblique fibromuscular membrane that divides the left atrium into two chambers: a postero-superior chamber that receives the pulmonary veins and an antero-inferior chamber that communicates with the mitral valve and left atrial appendage [147]. Cor triatriatum is thought to arise from incomplete incorporation of the common pulmonary vein into the primitive left atrium. *Sinus venosus ASDs* are associated with drainage of some, and less frequently all, of the right pulmonary veins into the right SVC or right atrium and normal connection of the left and other right pulmonary veins to the left atrium. Congenital *pulmonary vein stenosis* typically occurs at the pulmonary vein–left atrial junction but can be progressive in the length and degree of stenosis and number of pulmonary veins affected. The embryologic basis for this anomaly has been postulated to be abnormal incorporation of the common pulmonary vein into the left atrium [148].

KEY POINTS: DEVELOPMENT OF THE PULMONARY VEINS

- The lungs and tracheobronchial tree develop from a ventral outgrowth of the foregut.
- Establishment of a normal connection between the primary pulmonary vein and the left atrium is linked to the loss of the initial connection of the pulmonary venous plexus to the systemic veins.
- Abnormalities of pulmonary vein development result from failure of normal connections between rudimentary pulmonary venous structures to be established before the connections with the splanchnic venous system regress.

Systemic veins

By the end of the fourth week of development, the primitive venous system consists of three bilaterally symmetric systems that each drain into the right and left horns of the sinus venosus: the *vitelline* veins, which drain the yolk sac and gastrointestinal derivatives and will develop into the portal system; the *umbilical* veins, which carry oxygenated blood from the placenta and disappear after birth, and the *cardinal* veins, which drain the head, neck, and body wall and will develop into the caval system (Figure 6.23). The shift of the systemic venous return to the right atrium is associated with regression and remodeling to yield the adult asymmetrical venous pattern.

The vitelline and umbilical veins are altered by the development of the liver in the septum transversum and the formation of the hepatic sinusoids. The vitelline veins pass from the foregut through the septum transversum and developing liver to connect with the hepatic sinusoids (Figure 6.24). When the left horn of the sinus venosus regresses to form the coronary sinus, the proximal (near the heart) left vitelline vein also regresses, causing blood from the left side of the abdominal viscera to be channeled to the right side with subsequent enlargement of the right vitelline vein. The portion of the right vitelline vein between the liver and heart becomes the suprahepatic (terminal) portion of the IVC. During the second and third months of gestation, the right vitelline vein inferior to the liver becomes the portal vein and superior mesenteric vein, and some of the left-to-right vitelline anastomoses become the splenic and inferior mesenteric veins.

The umbilical veins, which initially pass on either side of the liver, become connected to the hepatic sinusoids. The right umbilical vein regresses during the second month of gestation, whereas the left umbilical vein loses its connection to the left horn of the sinus venosus and forms a channel, the ductus venosus, which connects it to the right vitelline vein.

The anterior (superior) cardinal veins, which drain the cephalic part of the embryo, and the posterior (inferior) cardinal veins, which drain the remainder of the embryo, join to form the common cardinal veins, which enter the respective horns of the sinus venosus. During the eighth week of gestation, the proximal (terminal) portion of the right anterior cardinal vein and the right common cardinal vein form the SVC

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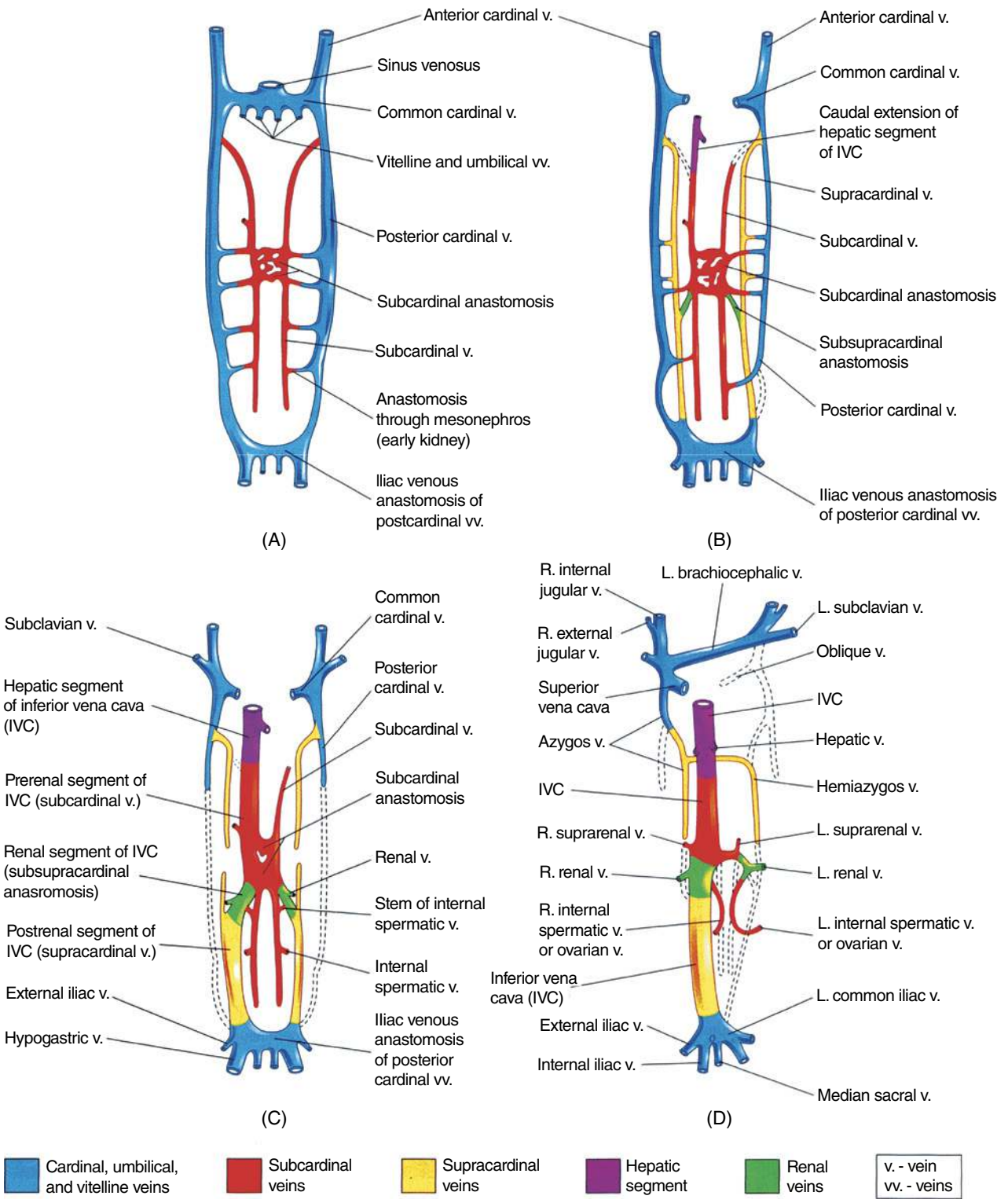


Figure 6.23 Illustrations of the primordial veins of bodies (trunks) of embryos (ventral views). Initially, three systems of veins are present: the umbilical veins from the chorion, vitelline veins from the umbilical vesicle, and cardinal veins from the body of the embryos. Next the subcardinal veins appear, and finally, the supracardinal veins develop. (A) At 6 weeks. (B) At 7 weeks. (C) At 8 weeks. (D) Adult. This drawing illustrates the transformations that produce the adult venous pattern. IVC, Inferior vena cava; L., left; R., right; v., vein; vv., veins. (Sources: Arey [149] and Moore et al. [131]. Reproduced with permission of Elsevier.)

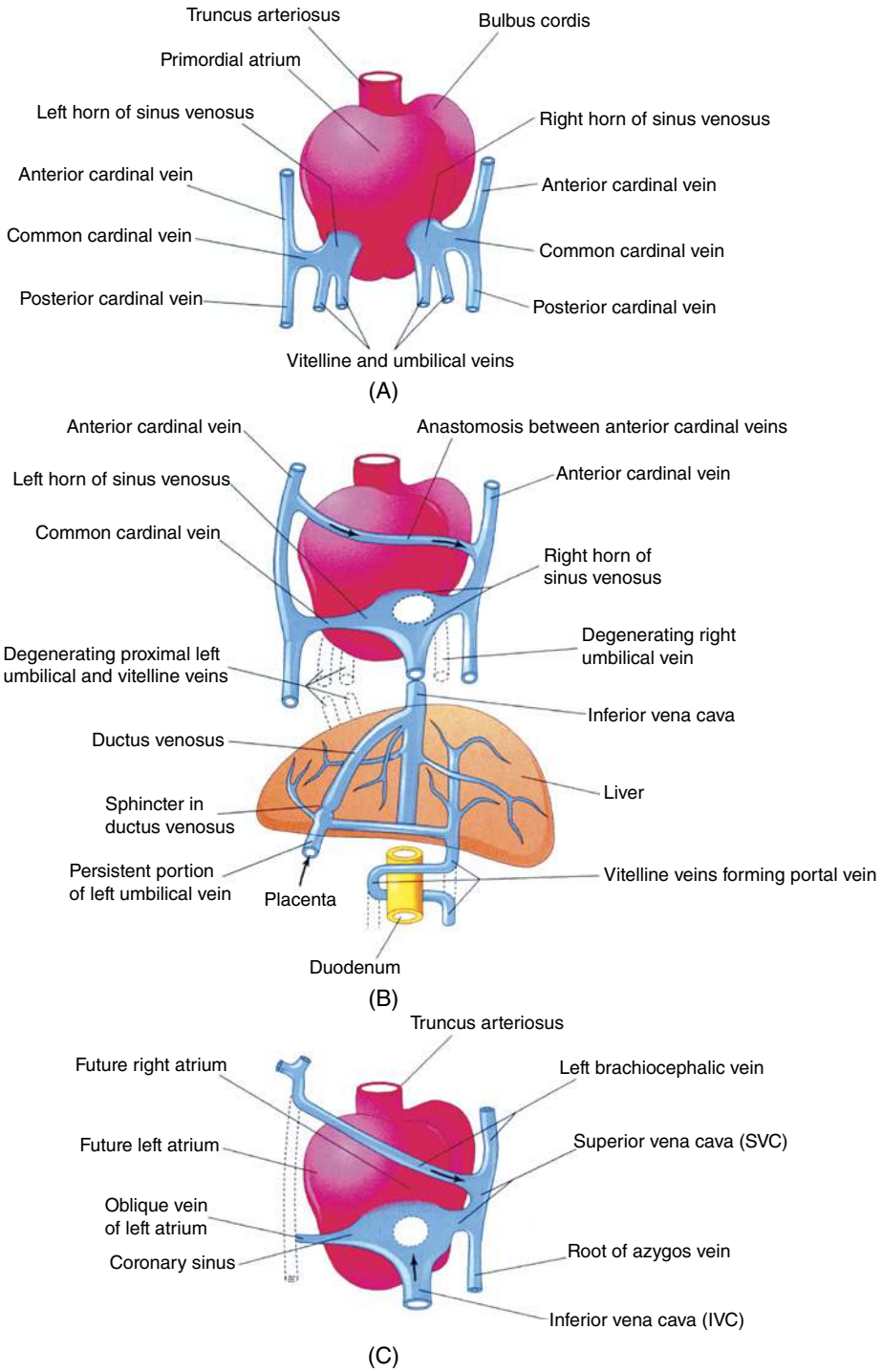


Figure 6.24 Dorsal views of the developing heart. (A) During the fourth week (approximately 24 days), showing the primordial atrium and sinus venosus and the veins draining into them. (B) At 7 weeks, showing the enlarged right sinus horn and venous circulation through the liver. The organs are not drawn to scale. (C), At 8 weeks, indicating the adult derivatives of the cardinal veins shown in (A) and (B). (Source: Moore et al. [131]. Reproduced with permission of Elsevier.)

(Figure 6.24). An anastomosis develops between the left and right anterior cardinal veins to form the left brachiocephalic (innominate) vein; the portion of the right anterior cardinal vein superior to the anastomosis will become the right brachiocephalic (innominate) vein. The terminal portions of the left anterior and common cardinal veins regress. Although a large portion of the posterior cardinal veins regresses, the right and left subcardinal veins sprout from the base of the posterior cardinal veins and grow caudally [150]. The left subcardinal vein regresses, but the right subcardinal vein

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loses its connection with the posterior cardinal vein and joins with the right vitelline vein to form the portion of the IVC between the liver and kidneys (prerenal segment). The right and left supracardinal veins also sprout from the base of the posterior cardinal veins and receive drainage from the intercostal veins. Together with a portion of the posterior cardinal veins, the right and left supracardinal veins form the azygos vein on the right and the hemiazygos vein on the left. The right supracardinal vein also anastomoses with the right subcardinal vein to form the portion of the IVC below the kidneys (renal segment). The sacral segment of the IVC is derived from the right and left posterior cardinal veins and the sacral segment connecting them. Thus, the IVC is made up of elements from four separate venous systems: the right vitelline vein between the liver and heart; the right subcardinal vein between the liver and kidneys; the right supracardinal vein below the kidneys; and the right and left posterior cardinal veins with the sacral segment connecting them.

Abnormalities of systemic vein development

The complex development of the venous system results in a wide spectrum of systemic venous anomalies. Heterotaxy syndromes result from disorders of left-right axis determination during early embryonic development and are frequently associated with systemic venous abnormalities [151]. Failure of the left anterior and left common cardinal veins to regress results in a *persistent left SVC* (LSVC), the prevalence of which is higher in patients with CHD. An LSVC may be found in association with a right SVC (*bilateral SVCs*) or may be the only SVC if the right anterior and right common cardinal veins have regressed. An LSVC will drain normally into the right atrium via the coronary sinus in the majority of cases, but it will drain into the left atrium if the coronary sinus is partially or completely unroofed. Bilateral SVCs with an unroofed coronary sinus usually occur in association with other congenital heart defects.

Failure of the hepatic segment of the IVC to form results in an *interrupted IVC* with azygos continuation into the right or left SVC; the hepatic veins in this setting drain directly into the right atrium. Multiple variations of *bilateral IVCs* can occur.

KEY POINTS: DEVELOPMENT OF THE SYSTEMIC VEINS

- The primitive systemic venous system consists of three bilaterally symmetric systems: the vitelline veins, the umbilical veins, and the cardinal veins.
- The shift of the systemic venous return to the right atrium is associated with regression and remodeling, resulting in the adult asymmetrical venous pattern.
- Alterations in the complex development of the venous system lead to a wide spectrum of systemic venous anomalies.

Development of cardiac innervation

The development and anatomy of cardiac innervation are complex and have been reviewed in detail previously [152, 153]. Neural crest cells give rise to the parasympathetic preganglionic neurons (cranial neural crest), the sympathetic chain, and sympathetic postganglionic neurons (truncal neural crest), and the ganglia and neurons of the intrinsic cardiac plexuses [154].

The heart has both sensory (afferent) and motor (efferent) innervation (148). Sensory information is relayed from the heart to the brain via both parasympathetic and sympathetic nerve pathways (Figure 6.25). One set of afferent nerves travels with the vagus nerve via the nodose ganglion (inferior ganglion of the vagus nerve) to the nucleus of the solitary tract in the brainstem. The second set of sensory nerves travels with the sympathetic nerves to the dorsal root ganglion and spinal cord. The parasympathetic afferents play a role in controlling both sympathetic and parasympathetic output, whereas the sympathetic afferents do not have any tonic influence over autonomic activity but are mostly nociceptive, as they are activated by coronary occlusion and register cardiac pain.

The motor (efferent) pathways are part of the autonomic nervous system, and both the parasympathetic and sympathetic pathways use preganglionic to postganglionic relays. Parasympathetic preganglionic neurons originate from the nucleus ambiguus and dorsal motor nucleus of the vagus in the medulla oblongata and use the vagus tracts to connect with postganglionic relays in the cardiac ganglia. Sympathetic preganglionic neurons originate in the intermediolateral column in the thoracic spinal cord and synapse with postganglionic neurons in the ganglia of the lower cervical and upper thoracic sympathetic chain [153].

The cardiac plexuses are an accumulation of mixed neurons, both efferent and afferent, on the epicardial surface near the arterial and venous poles. These plexuses comprise ganglia that are interconnected by local neuronal circuits and regulate control of regional cardiac function [153]. The ganglia have an intrinsic activity that is modulated by sympathetic and parasympathetic (vagal) inputs. Postganglionic parasympathetic nerves extend to the SA and AV nodes to innervate the cardiac conduction system [152]. Innervation of myocardial cells in the right atrium is predominantly cholinergic and that of the left atrium and left and right ventricles is predominantly adrenergic [155].

The cardiac nervous system develops and matures slowly and is not fully functional until well after birth [154]. Parasympathetic innervation precedes sympathetic innervation, so the parasympathetic–cholinergic system becomes functional before the sympathetic–adrenergic system. Autonomic receptor-mediated effector mechanisms are present before functional innervation (pre-innervation phase), thereby allowing a cardiac response to circulating catecholamines to mitigate the effects of hypoxia and bradycardia [152].

Abnormalities of cardiac innervation

Development of cardiac innervation during the fetal period can be associated with innervation abnormalities in adult life [152].

Dysautonomias result from impaired autonomic interactions due to inadequate development, migration, survival, and function of sensory and autonomic neurons; the sympathetic

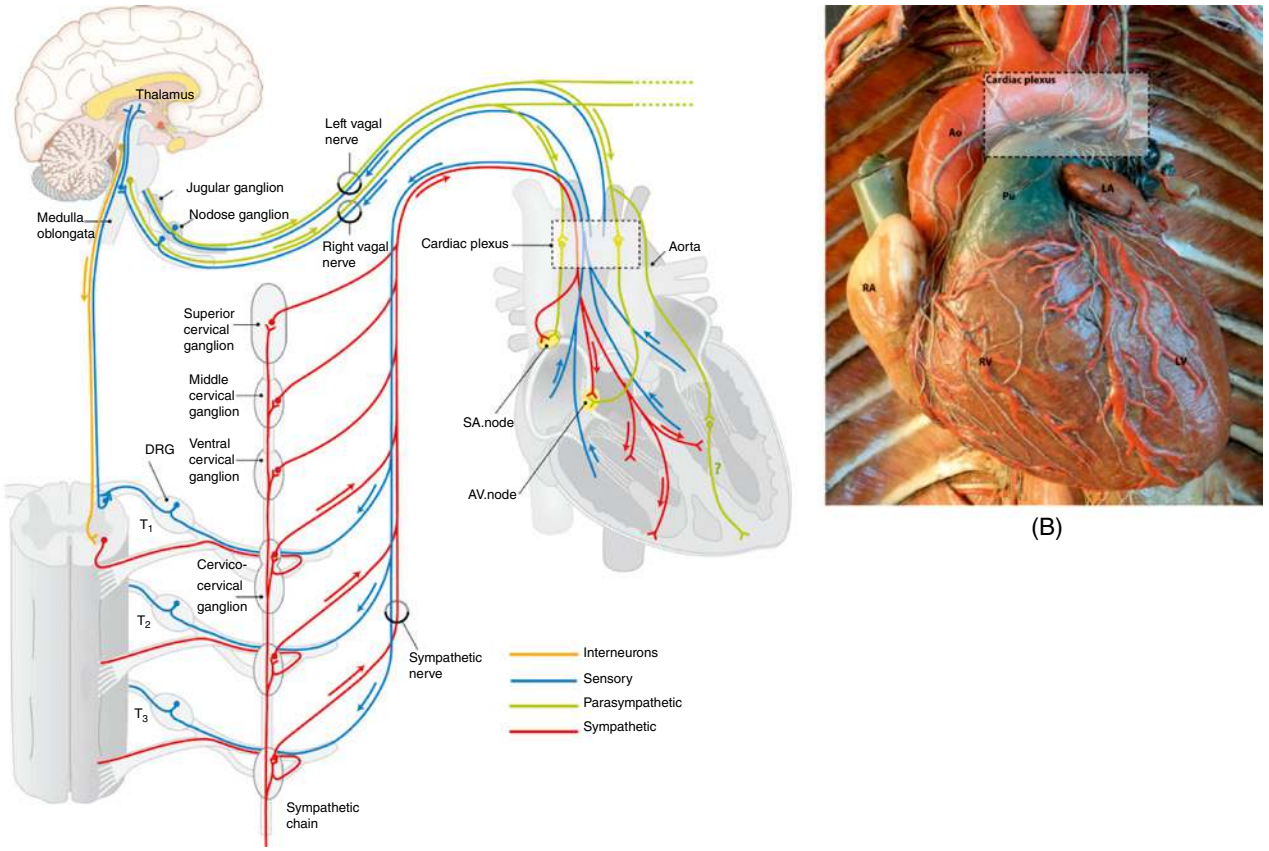


Figure 6.25 Overview of cardiac innervation. (A) Schematic drawing of the cardiac visceral innervation system. Cardiac innervation starts with a signal from the heart or baroreceptors (e.g., on the aorta), relayed by sensory nerves (blue) giving feedback on, for instance, the levels of oxygen, carbon dioxide and blood pressure. The brain will give a signal to parasympathetic or sympathetic nerves to either relax or stimulate the heart. Parasympathetic innervation is achieved mainly via the vagal nerve (green) that will synapse in cardiac ganglia from where postganglionic nerves innervate the SA node and AV node, and potentially ventricular myocytes. Sympathetic neurons (red) start in the grey matter of the spinal cord, where interneurons (orange) from the brain project to the sympathetic neurons. Via the ventral root of the spinal cord, sympathetic nerves synapse in the sympathetic chain, from where postganglionic nerves will enter the heart. (B) This wax mold shows how cardiac nerves enter via the cardiac plexus and follow cardiac vessels over the heart. Courtesy of: Museo delle Cere Anatomiche "Luigi Cattaneo", University Museum System, Alma Mater Studiorum—University of Bologna, picture taken by Dr. E.A.J.F. Lakke. Ao, aorta; DRG, dorsal root ganglion; LV, left ventricle; Pu, pulmonary artery; RA, right atrium; RV, right ventricle. (Source: Végh et al. [152]. / MDPI / CC BY 4.0).

neurons are affected more often than the parasympathetic neurons [156]. *Familial dysautonomia* (Riley–Day syndrome) is the best known of the hereditary sensory and autonomic neuropathies and is associated with orthostatic hypotension and an increased risk of sudden death. It is caused by mutations of the IKAP gene on chromosome 9q31 which affects the development of neurons and is associated with catecholamine hypersensitivity [157, 158].

Sudden infant death syndrome has been linked to abnormal development of the autonomic nervous system, with the final pathway thought to involve immature cardiorespiratory autonomic control with failure of the arousal responsiveness from sleep [159]. Multiple underlying candidate genes have been identified [160].

Autonomic dysfunction is present in individuals with Down syndrome as shown by chronotropic incompetence, reduced heart rate and blood pressure responses to autonomic tasks, and low work capacity [161–163]. This dysfunction may or may not be present at rest [164]. The risk of bradycardia is increased during induction of anesthesia in children with Down syndrome [165].

KEY POINTS: INNERVATION OF THE DEVELOPING HEART

- The heart has both sensory (afferent) and motor (efferent) innervation.
- The cardiac nervous system develops and matures slowly and is not fully functional until well after birth.

- Parasympathetic innervation precedes sympathetic innervation.
- Abnormalities in cardiac innervation may result from impaired autonomic interactions and abnormal development of the autonomic nervous system.

Development of the cardiac lymphatics

The heart has an extensive evolutionarily conserved lymphatic network. As reviewed by Gancz and colleagues, myocardial contractions force lymph in a unidirectional fashion from lymphatic capillaries in the endocardium and myocardium through extensive collecting vessels to the epicardium [166]. The lymph is then drained from the apex to the base and ultimately to the mediastinal lymph nodes. A reduction in lymph flow rate or an increased microvascular permeability leads to interstitial edema and myocardial dysfunction [167].

Lymphatic capillaries sprout from the mediastinal lymphatics around the eighth embryonic week [166]. By the beginning of the fourth month, these capillaries have extended from the base of the heart along the coronary arteries to cover most of the epicardial surface. Inward lymphatic growth then takes place in the myocardium and epicardium. Although the development of the cardiac lymphatic system ends prenatally, myocardial infarction is associated with a strong lymphangiogenic response in the infarcted zone [168]. Therapeutic strategies to boost this lymphangiogenesis are being evaluated to promote heart regeneration.

Summary

Table 6.2 shows the stages of human development and provides a timeline of the corresponding events in the development of the cardiovascular system, summarizing the information discussed in this chapter [26]. Four cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) are derived from the mesoderm to form the building blocks of the heart and vascular system (Figure 6.26) [30]. Cardiac neural crest cells are critical to the formation and remodeling of the aortic arch arteries, outflow tract septation, semilunar valvulogenesis, cardiac neuronal tissue, and the insulation of the conduction system [169]. Reactivation of cardiac stem cells has opened the door for using regenerative medicine and novel therapies for treating congenital and acquired heart disease [11].

Table 6.2 Stages of human development with corresponding events in cardiac development

Carnegie stage	Human DPC	Mouse DPC	
CS8	17–19	7	The cardiac crescent forms
CS9	19–21	7.5	The embryo folds, the pericardiac cavity is placed in its final position, the gully of myocardium forms, the endocardial plexus forms, cardiac jelly forms
CS10	22–23	8	The heart beats, the endocardial tubes fuse, the **mesocardium** perforates, looping starts, the ventricle starts ballooning
CS11	23–26	8.5	The atria balloon, the pro-epicardium forms
CS12	26–30	9.5	The septum primum appears, the right venous valve appears, the muscular part of the ventricular septum forms, cells appear in the cardiac jelly, the epicardial growth starts
CS13	28–32	10.5	The atrioventricular cushions form, the pulmonary vein attaches to the atrium, the left venous valve appears, epicardial mesenchyme appears first in the atrioventricular sulcus
CS14	31–35	11.5	The atrioventricular cushions form, the pulmonary vein attaches to the atrium, the left venous valve appears, epicardial mesenchyme appears first in the atrioventricular sulcus
CS15	35–38	12	The atrioventricular cushions approach one another, the outflow ridges become apparent, capillaries form in the epicardial mesenchyme
CS16	37–42	12.5	The primary atrial septum closes, the outflow tract ridges approach the interventricular septum. The entire heart is covered in epicardium
CS17	42–44	13.5	Secondary atrial septum appears, the sinus node becomes discernible, the left and right atrioventricular connections become separate, the proximal outflow tract becomes septated, the semilunar valves develop
CS18	44–48	14.5	Papillary muscles appear, the atrioventricular valves start to form
CS19	48–51	15	The left venous valve fuses with the secondary septum, the mural leaflets of the mitral and tricuspid valve are released
CS21	53–54	16	The main branches of the coronary artery become apparent
CS22	54–56	16.5	The chordae tendinae form
CS23	56–60	17.5	The septal leaflet of the tricuspid valve delaminates

DPC, days *post coitum*.

Source: Sylva et al. [26]. Reproduced with permission of John Wiley & Sons.

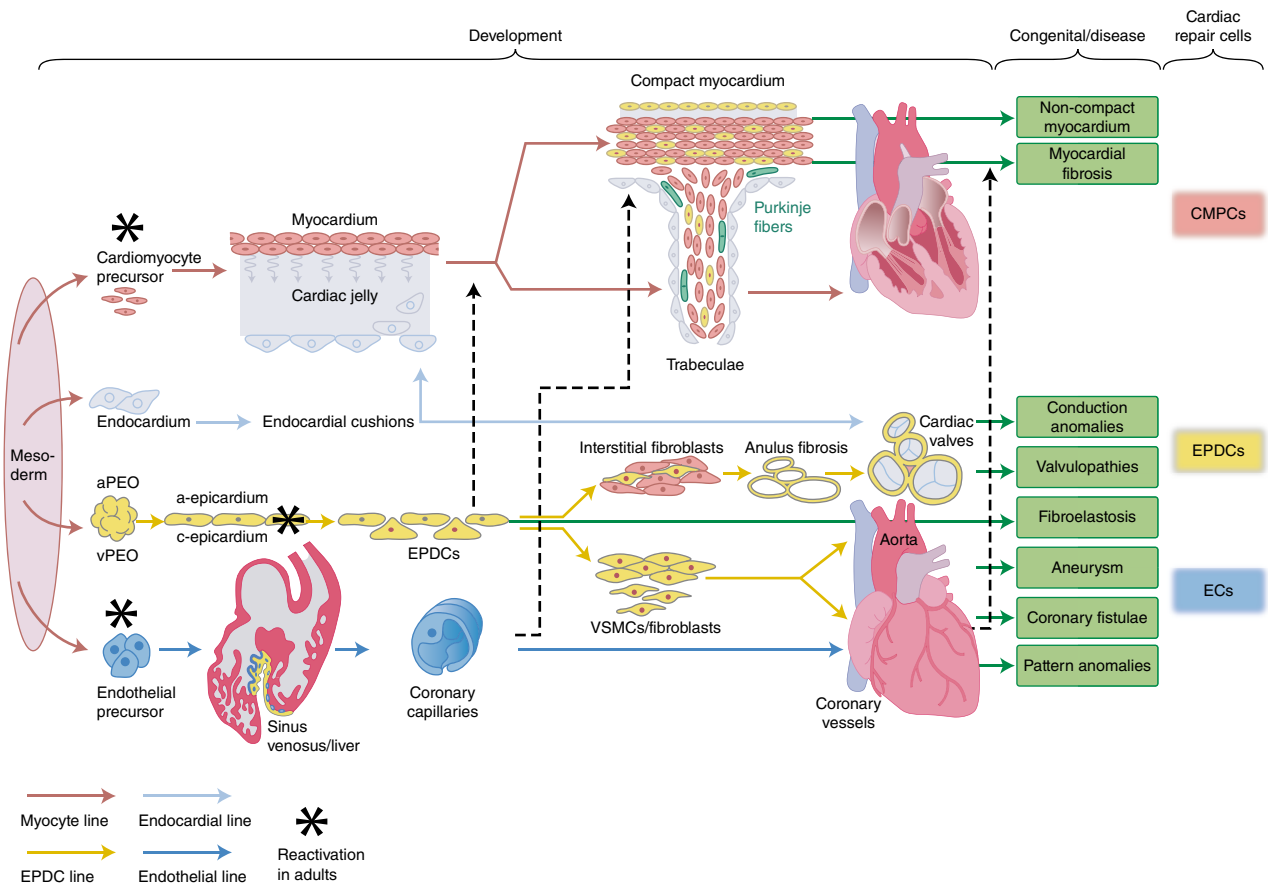


Figure 6.26 Schematic presentation of cellular contribution to heart development with special focus on the role of epicardium and epicardially derived cells (EPDCs) during normal development, disease, and repair processes. Four mesodermal cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) are considered to form the main building blocks of the heart. The differentiation of each line is depicted together with the main interactions with the other cell lines. The most frequent EPDC-related congenital malformations and (acquired) disease processes are boxed in green, while three cardiac (stem) cell populations that may become reactivated are presented on the far right. aPEO, arterial proepicardial organ; vPEO, venous proepicardial organ; a-epicardium, arterial epicardium (from aPEO); c-epicardium, complete epicardium (from vPEO); VSMCs, vascular smooth muscle cells; CMPCs, cardiomyocyte progenitor cells; ECs, endothelial cells. (Source: Gittenberger-de Groot et al. [30]. Reproduced with permission of Elsevier.)

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

11 Srivastava D. Reprogramming approaches to cardiovascular disease: from developmental biology to regenerative medicine. In: Nakanishi T, Markwald RR, Baldwin HS, Keller BB, Srivastava D, Yamagishi H (eds). Etiology and Morphogenesis of Congenital Heart Disease: From Gene Function and Cellular Interaction to Morphology. Tokyo, Japan: Springer Japan, 2016, pp. 3–10. Review of the cardiac developmental biology discoveries that underpin direct reprogramming of cardiac fibroblasts into cardiomyocyte-like cells for addressing cardiac regeneration and treatment of heart disease.

17 Meilhac SM, Buckingham ME. The deployment of cell lineages that form the mammalian heart. Nat Rev Cardiol 2018;15(11):705–24. Review of the diverse origins of cardiac cell types and the lineage relationships between cells of a given type that contribute to different parts of the heart.

25 Morton S, Roberts AE. Genetic basis of congenital heart disease. NeoReviews 2015;16(6):e340–52. Basic review of the genes important in heart development and current techniques for evaluating possible genetic causes of congenital heart disease in the neonate.

35 Kirby ML. Molecular Control of Looping. Cardiac Development. Oxford, UK: Oxford University Press, 2007, p. 87–102. Excellent textbook by a leader in the field providing a well-rounded perspective on all aspects of cardiac development. Recommended to those interested in cardiac embryology and wishing to move beyond the basic medical embryology.

48 Piera-Velazquez S, Jimenez SA. Endothelial to mesenchymal transition: role in physiology and in the pathogenesis of human diseases. Physiol Rev 2019;99(2):1281–324. In-depth review of the important process of EndMT with respect to its participation in key embryonic developmental processes and in the pathogenesis of many inherited and acquired diseases including malignant, vascular, inflammatory, and fibrotic disorders.

98 Parker LE, Landstrom AP. Genetic etiology of left-sided obstructive heart lesions: a story in development. J Am Heart Assoc 2021;10(2):e019006. A basic science review for clinicians of the genes and variants associated with the different left-sided obstructive lesions with a discussion of the research avenues needed to bridge the gaps in our current understanding of the genetic basis of nonsyndromic congenital heart disease.

126 Skinner JR, Winbo A, Abrams D, et al. Channelopathies that lead to sudden cardiac death: clinical and genetic aspects. Heart Lung Circ 2019;28(1):22–30. A clinically relevant review of the genetics,

cellular mechanisms, risk stratification, and treatment of channelopathies that can lead to sudden cardiac death.

142 Bökenkamp R, DeRuiter MC, van Munsteren C, Gittenberger-de Groot AC. Insights into the pathogenesis and genetic background of patency of the ductus arteriosus. Neonatology 2010;98(1):6–17. Review of the complex pathogenesis and genetic background of patent ductus arteriosus with the aim of developing better management strategies in premature infants, CHD with ductal-dependant circulations, and patients with syndromic and non-syndromic PDA.

152 Végh AMD, Duim SN, Smits AM, et al. Part and parcel of the cardiac autonomic nerve system: unravelling its cellular building blocks during development. J Cardiovasc Dev Dis 2016;3(3):28. Highly detailed review of the development of the cardiac autonomic nervous system (cANS). A later publication by the same authors discusses the anatomy of the cANS with respect to the clinical aspects for neuraxial modulation (thoracic epidural anesthesia, cardiac sympathectomy) [153].

164 Carvalho TD, Massetti T, Silva TDD, et al. Heart rate variability in individuals with Down syndrome – A systematic review and meta-analysis. Auton Neurosci 2018;213:23–33.The autonomic dysfunction in patients with Down syndrome is highlighted in the context of a systematic review and meta-analysis of heart rate variability, thereby providing a better understanding of the bradycardia associated with induction of general anesthesia.

CHAPTER 7

Nomenclature and Anatomic Evaluation in Congenital Heart Disease

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Introduction

It is well recognized that the large number, wide spectrum, and complex nature of congenital malformations of the cardiovascular system can make it quite challenging to understand the corresponding structural abnormalities and their associated functional and hemodynamic consequences. This issue can be further complicated by the seemingly bewildering nomenclature and classification systems used in congenital and pediatric cardiology. In addition, the diverse terminology (at times, different terms can even be used to refer to the same anatomic structure, pathologic finding, or lesion) and the numerous classification schemes for categorizing individual anomalies can pose obvious difficulties [1, 2]. This variable taxonomy can be confusing for many, but it is even more perplexing for individuals with limited knowledge or familiarity with the subject, further adding to the intimidating aspects of congenital heart disease (CHD).

Many clinicians have acknowledged the critical need for a consistent nomenclature and classification system for CHD that can be widely accepted by all disciplines involved in the care of these patients. As far back as the late 1970s, Shinebourne et al. indicated that "for a nomenclature system to be of value, it needed to be capable of describing any combination of cardiac malformations which may be encountered" [3]. It was also noted that the scheme "should allow for precise classification of such malformations during a patient's life." The lack of a consistent nomenclature for describing the various defects or uniform classification scheme for CHD continues to be a source of frustration and confusion in everyday practice. Work in this area is still ongoing but over the last several years significant progress has been made in the development of comprehensive standardized nomenclature and a classification code with the goal of unifying the terminology for pediatric and congenital cardiac care as will be highlighted in this chapter.

An understanding of the approaches developed to describe CHD and the elements considered in the morphologic assessment of the heart are important aspects of the practice of pediatric/congenital cardiac anesthesiology. This chapter provides a brief overview of the essential steps involved in anatomic evaluation in CHD. It addresses the segmental analysis of the heart and other relevant components of the diagnostic assessment of the congenitally malformed heart, but it does not dwell on the specifics of one

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language or taxonomy over the other for describing CHD. Thus, the discussion is not meant to be comprehensive but, instead, it aims to emphasize important points related to the structural evaluation of a patient with CHD. A discussion of the various classification systems for congenital cardiac lesions is beyond the scope of this chapter but is addressed in various chapters throughout this textbook.

Congenital heart surgery nomenclature and database project

In the late 1990s, the Society of Thoracic Surgeons, in collaboration with The European Association for Cardiothoracic Surgery, launched the International Congenital Heart Surgery Nomenclature and Database Project with the hope of standardizing the nomenclature used for CHD. One of the goals was to establish a foundation to facilitate multi-institutional analysis of patient outcomes. This effort led to the adoption of a common nomenclature and classification system of pediatric and CHD by these professional organizations [4]. Concurrently, another international nomenclature system, the European Paediatric Cardiac Code, was developed for congenital cardiac disease [5, 6]. In 2000, The International Nomenclature Committee for Pediatric and Congenital Heart Disease was created, which evolved into a society with various components, including a Nomenclature Working Group. As a result, the *International Pediatric and Congenital Cardiac Code* (IPCCC) was eventually developed, which allowed for cross-mapping of the two nomenclature systems for CHD [7]. The aim of the project was to provide an all-inclusive, internationally accepted, cohesive, and comprehensive system for describing pediatric cardiovascular diseases and CHD using a common nomenclature. This undertaking would ultimately enhance communication among healthcare providers; facilitate education, research, and patient care; and allow for multicenter assessment of clinical outcomes, quality assurance, risk stratification, and many other important benefits. In fact, the IPCCC nomenclature and classification code, in conjunction with the database created by the International Congenital Heart Surgery Nomenclature and Database Project can be freely downloaded from the internet (www.ipccc.net) and is currently being used worldwide. It has served as a resource in extensive surgical outcome analyses involving large numbers of patients. The reader is referred to various publications related to these projects, which address the nomenclature for specific defects, consensus definitions for several complex cardiac anomalies, classification schemes, and applications [8–24]. Ongoing collaborations with the World Health Organization, other international groups addressing standard medical terminology, and the health care industry, are likely to further advance this effort. In fact, this classification system has been accepted for incorporation into the 11th iteration of the International Classification of Diseases (ICD-11], representing a major step for further standardization of nomenclature across the globe [23, 25]. Despite the remarkable efforts to establish a comprehensive standardized nomenclature and hierarchical classification system, it is well recognized that ongoing debate and discussion will continue to take place in clinical practice while these schemes continue to be refined [24].

KEY POINTS: THE INTERNATIONAL PEDIATRIC AND CONGENITAL CARDIAC CODE (IPCCC)

- When initially developed, the IPCCC allowed for cross-mapping of two different nomenclature systems for CHD.
- The goal of this effort was to overcome the limitations of various nomenclature systems by creating a comprehensive and consistent common language.
- The IPCCC is used widely today and represents a standardized international nomenclature and classification system for pediatric and congenital heart disease.
- This classification system has been accepted by the WHO for incorporation into the 11th iteration of the ICD coding system (ICD-11 code).

Approaches for describing congenital heart disease

Several publications have addressed, in detail, the applications of an organized anatomic analysis in the diagnosis of CHD and the steps involved in a comprehensive structural assessment [3, 26–33]. The *segmental approach*, as initially described by Richard Van Praagh and colleagues in the 1960s, relies upon an examination of cardiac anatomy in a series of segments or "building blocks" [34, 35]. These major units are considered the essential components of the heart, whether normal or diseased [26]. The anatomy of the various cardiac segments and their relationships to each other represent the foundation of the segmental analysis. Robert Anderson and colleagues expanded upon this concept but reduced the emphasis on relationships by proposing a scheme based on blood flow through the heart, which focused on characterizing the connections between the segments [28, 32]. Based on this approach, the *sequential segmental approach* was developed.

The detailed methodology used in the sequential segment-by-segment approach allows for a stepwise examination of all cardiac segments by navigating through the heart in the direction of blood flow from the atria to the ventricles to the great arteries. The three main segments are the veins and atria, ventricles, and great arteries. The units are joined to each other by two connecting cardiac segments (or junctions): the atrioventricular (AV) junction (AV canal region), which connects the atria to the ventricles, and the ventriculoarterial (VA) junction (infundibulum/conus arteriosus), which connects the ventricles to the great arteries (Figure 7.1). This systematic examination offers an organized and rigorous method that facilitates the defining of congenital cardiovascular defects. The benefit of this analysis is that it can be applied to all congenital cardiac malformations, although it is particularly useful for characterizing complex defects. The merits of this approach are reflected in the fact that this system has been incorporated into clinical use within various disciplines related to CHD and applied in the evaluation of fetuses to adults [36–42].

The "Van Praaghian" and "Andersonian" nomenclature systems

Historically, and based on the development of the nomenclature as previously described, there have been two major

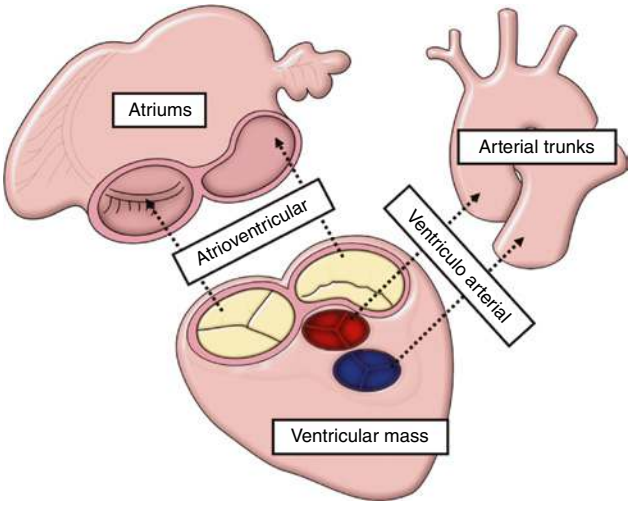


Figure 7.1 Sequential segmental analysis. Figure depicts the key components of the sequential segmental analysis: the three major building blocks (atria, ventricles, arterial trunks) and their joining segments (atrioventricular and ventriculoarterial junctions). (Source: Ms. Gemma Price. Reproduced with permission.)

philosophies regarding the segmental assessment of the congenitally malformed heart. These schools of thought have been led by two world-renowned leaders in the field: Drs. Richard Van Praagh and Robert H. Anderson. Colloquially, these have been referred to as the "Van Praaghian" and "Andersonian" nomenclature systems. The Van Praagh classification system was pioneered and evolved in Boston, Massachusetts and is widely used in North America, whereas that by Anderson was developed and is conventional throughout Europe.

Although these approaches to describe cardiac anatomy share common elements, there are many important differences. A significant one relates to the shorthand notation used in the Van Praagh system to facilitate communication among providers involved in the diagnosis and management of patients with CHD as described to follow. Other divergent viewpoints include terminology and the methods used to describe morphology and cardiac pathology. The disparities between the two major schools of nomenclature have created disagreements among advocates and specialists in the field, sometimes resulting in heated arguments and controversies between the different camps. Efforts have been made to reconcile these two approaches in recognition of the fact that both of these systems have virtues and that, in many ways, they may complement each other [43, 44]. The reader is referred to the excellent resource entitled *Atlas of Congenital Heart Disease Nomenclature: An Illustrated Guide to the Van Praagh and Anderson Approaches to Describing Congenital Cardiac Pathology* for an in-depth discussion on these two nomenclature systems [45].

Although clinicians have generally been divided as followers of the teachings of one school or the other, many practitioners have opted for a stance somewhere in the middle recognizing that the likelihood of implementing a single, universally accepted system is remote, and they continue to see merits in the various schemes currently used [46]. It should also be recognized that even these systems have evolved in their thinking over time [47]. In some cases, an alternate approach has been to simply describe the anatomy without regard for either system. Despite personal preferences, the expectation in most cases is for providers of CHD patients to be fluent in these nomenclature systems. It should be emphasized that regardless of the nomenclature or scheme favored, it is more important that each institution has a uniform and consistent approach for describing and referring to the various defects or structural abnormalities to optimize communication among all practitioners involved in patient care.

The Van Praagh notation

A unique feature of the Van Praagh style is the use of a three-letter notation, or code, enclosed in braces or curly brackets {X,X,X}. The letters in the set are abbreviations separated by commas that represent the sidedness or anatomical organization (referred to as "situs") of the three main cardiac segments of the heart in venoarterial sequence (atria, ventricles, great arteries) [2, 30]. In essence, the segments are to be considered in terms of the following:

- the atrial situs or sidedness of atrial chambers
- ventricular loop (ventricular topology)
- spatial relationship of the arterial trunks

The possibilities for each segment are denoted by different letters as shown in Box 7.1 (also refer to the discussion later in the chapter).

The normal anatomic configuration would be indicated by the notation coding of {S,D,S}. This notation corresponds to visceroatrial situs solitus or {S,-,-} with the vena cavae and the morphologic right atrium on the right side, and the morphologic left atrium on the left side; D-loop ventricles {-,D,-} where the right ventricle is right-handed, rightward and anterior to the morphologic left ventricle, whereas the left ventricle is left-handed, leftward and posterior as a result of a cardiac tube curved rightward (dextro or D-loop); and normal situs solitus of the great arteries {-,-,S} where the pulmonary artery is located anterior and leftward to the aorta. This shorthand system does not specify the "alignments" (AV or VA) between the cardiac segments, a term preferred by Van Praagh

Box 7.1: Van Praagh notation

In the Van Praagh notation the letters are abbreviations that represent the sidedness or anatomical organization (referred to as situs) of the three main cardiac segments of the heart in venoarterial sequence (atria, ventricles, and great arteries).

- *For the atrial situs (first letter)*:
  - "S" for "situs solitus" (normal arrangement)
  - "I" for "situs inversus" (mirror image arrangement)
  - "A" for "situs ambiguus"
- *For the ventricular loop (second letter)*:
  - "D" for "D-loop" (rightward orientation)
  - "L" for "L-loop" (leftward orientation)
  - "X" for cases where looping cannot be defined
- *For the position and relationship of the great arteries (third letter):*
  - "S" for normally related
  - "I" for inverted or mirror image relationship
  - "D" for D-transposed or malposed great arteries, with aorta to the right of the main pulmonary artery
  - "L" for L-transposed or malposed great arteries, with the aorta to the left of the main pulmonary artery
  - "A" for the aorta directly anterior to the main pulmonary artery

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over "connections," nomenclature favored by Anderson, to describe the segments between the atrial and ventricular chambers, and the ventricles and great arteries. In this system, the segmental alignments are noted separately [30, 31, 48]. As per Van Praagh, "significant abnormal VA alignments such as transposition of the great arteries (TGA) are indicated *before* the braces: TGA {-,-,-}," while "important abnormal segmental connections and other associated cardiovascular anomalies are listed *after* the braces: {-,-,-} with straddling tricuspid valve and ventricular septal defect of the AV canal type" [2].

At first glance, this nomenclature system may appear relatively straightforward and easy to understand, in fact, it has been widely utilized in many aspects of diagnostic imaging including echocardiography and radiology [41, 42]. However, the combination of letters can be somewhat complex to decode or interpret, particularly for individuals who are not familiar with the shorthand nomenclature. In addition, although the segmental classification scheme can be used to describe most congenital heart defects, some anomalies, such as heterotaxy syndromes, can be difficult to define precisely using this scheme. Therefore, even though it is well recognized and widely applied, this system has not been universally embraced. Some consider a more descriptive approach less likely to cause confusion, particularly, in the case of complex CHD [49].

KEY POINTS: APPROACHES FOR DESCRIBING CHD

- The sequential segmental approach is the essence of diagnostic assessment for CHD.
- This approach allows for a stepwise examination of all cardiac segments by navigating through the heart in the direction of blood flow.
- There are two major philosophies regarding the segmental assessment of the congenitally malformed heart: one led by Dr. Richard Van Praagh and the other by Professor Robert H. Anderson.
- An alternate approach consists of describing the anatomy without regard for either system, particularly in the case of complex CHD.
- It is more relevant for each institution to have a uniform and consistent system for describing and referring to the various congenital cardiac anomalies.

Segmental approach to diagnosis of congenital heart disease

For many decades, and with both the Van Praagh or Anderson systems, the *segmental approach* has been used to characterize congenital anomalies that affect the heart and related vascular structures [3, 26]. The steps taken in this segmental analysis are described in the sections that follow.

Cardiac position and apex orientation

The aspect of CHD evaluation related to cardiac position can be confusing because it is described differently by various sources and the terminology used (Figure 7.2). One approach describes the cardiac position as the spatial location of the majority of the cardiac mass within the thoracic cavity, using the sternum as the midline reference. The term *levocardia* indicates that the heart occupies most of the left hemithorax (i.e., a left-sided heart), *dextrocardia* indicates that the heart is in the right hemithorax (i.e., right-sided heart), and *mesocardia* indicates that the heart is in the midline position. In addition, a distinction is made between primary and secondary dextrocardia; the former is due to a structural cardiac defect, whereas the latter results from the heart being displaced by extracardiac conditions.

A second approach specifies both the cardiac position and orientation, as these are not to be considered synonymous when describing cardiac location. In this scheme, as in the previously mentioned approach, cardiac position refers to the overall location of the cardiac mass relative to the midline; however, the terminology is used differently. In this algorithm, the terms *levoposition*, *dextroposition*, and *mesoposition* are used to indicate that the cardiac mass is predominantly in the left hemithorax, right hemithorax, or middle, respectively. Furthermore, the terms levocardia, mesocardia, and dextrocardia are used to describe cardiac orientation, or alignment from the base (great arteries) to the apex (ventricular apex), instead of cardiac position. Levocardia indicates that the heart's cardiac apex points to the left side of the chest, mesocardia indicates that the heart's cardiac apex points straight inferiorly, and dextrocardia indicates that the heart's apex points to the right. Displacement of the heart into the right or left thoracic cavity is described as *dextropositioning* or *levopositioning*, respectively. Other terminology used related to the orientation of the cardiac apex is "levoversion" if it points to the left and "dextroversion" if it points to the right.

In most cases, the cardiac position and base-to-apex orientation are in agreement, meaning that both are aligned in the same direction. For example, in the case of the normal heart, the cardiac mass is in the left hemithorax and the ventricular apex is directed towards the left. Consequently, the distinction between these two parameters is irrelevant in most cases. However, when the heart is displaced, for example by the presence of abdominal contents in an infant with a congenital left diaphragmatic hernia, the cardiac mass may be pushed to the right hemithorax (dextroposition), while the cardiac apex still points to the left (levocardia). In such cases, the two descriptors should be noted. At times, these features are critically important for surgical planning.

It should be recognized that cardiac position and apex orientation cannot be utilized to establish cardiovascular anatomy, nor do these have a predictable relationship to cardiac pathology. A good example of this issue is the patient with dextrocardia in which complex CHD may be found or in some instances, a structurally normal heart.

KEY POINTS: CARDIAC POSITION AND APEX ORIENTATION

- Cardiac position refers to the spatial location of the majority of the cardiac mass within the thoracic cavity.
- Cardiac orientation refers to the alignment from the base (great arteries) to the apex (ventricular apex).
- In most cases, the cardiac position and base-to-apex orientation are in agreement.

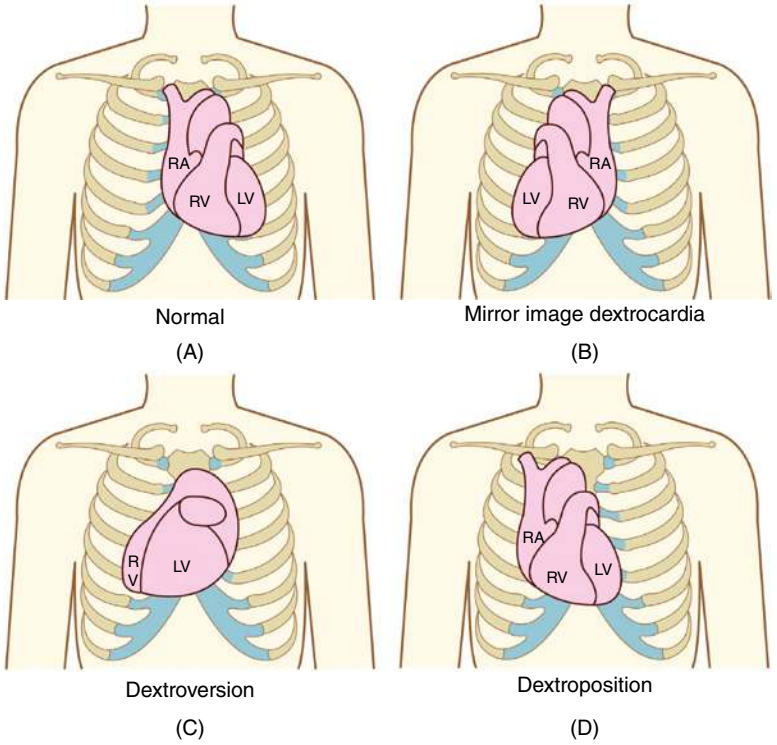


Figure 7.2 Pictorial representation of an anteroposterior view of the thorax showing (A) the normal position of the heart, (B) mirror image dextrocardia, (C) dextroversion, and (D) dextroposition. (Source: Ahmad et al. [50]. Reproduced with permission of Elsevier.)

Visceral and atrial situs

The first step of the sequential analysis, before defining the cardiac structures, is evaluating the anatomic relationships of the viscera (i.e., the abdominal and thoracic organs). This is referred to as determining the *visceral situs*, or pattern of anatomic organization (meaning sidedness). In clinical practice, to determine the visceral situs, the abdominal viscera are examined, focusing on the position of the liver, stomach, spleen, and abdominal great vessels (i.e., the aorta and inferior vena cava [IVC]). This examination is primarily performed using ultrasonography. The situs of the thorax can be evaluated by assessing bronchial morphology, as determined, for example, by chest radiography.

In the human body, there are distinct left-sided and right-sided structures [51]. In the normal arrangement, the liver is on the right side of the body, whereas the stomach and spleen are on the left. There is also a distinctive pattern to each lung in terms of lobes, anatomy of the bronchi, and course of the bronchi with respect to the associated pulmonary artery. The normal anatomic layout is characterized as follows: the right lung comprises three lobes, a short main bronchus, and a course of the bronchus above the right pulmonary artery (eparterial), whereas the left lung comprises two lobes and a longer left main bronchus (as compared with the right bronchus) that courses below the left pulmonary artery (hyparterial).

The normal (usual) arrangement of the thoracoabdominal organs is referred to as *visceral situs solitus*. In contrast, the mirror image arrangement, in which the left–right position and orientation of the organs is reversed, is referred to as *visceral situs inversus*. A third type of arrangement is referred to as *situs ambiguus* (Latin spelling; the term "situs ambiguous" commonly used, as in this chapter), which is defined in Van Praagh's school as "an abnormality in which there are components of situs solitus and situs inversus in the same person" [17]. In both situs solitus and situs inversus, an asymmetric pattern of the abdominal/thoracic organs is present. In contrast, in situs ambiguous there is symmetry of the abdominal/thoracic organs, but their position/orientation is variable. It has been proposed that "situs ambiguous can be considered to be present when the thoracic and abdominal organs are positioned in such a way with respect to each other as to be not clearly lateralized and thus have neither the usual, or normal, nor the mirror-imaged arrangements" [17]. When this arrangement occurs, there is a tendency towards duplication of either right-sided or left-sided structures. This abnormal anatomic organization is frequently found within the context of *heterotaxy*, which is defined as "an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body" [17]. In heterotaxy syndromes, a spectrum of cardiac and extracardiac anomalies can be present, including absence of lateralization of the abdominal viscera, lack of a spleen or presence of multiple spleens (*asplenia* and *polysplenia syndromes*), and rotation defects of the gastrointestinal system, among other defects.

Atrial situs is a term used to describe the arrangement of the atria as determined by the position of the morphologic

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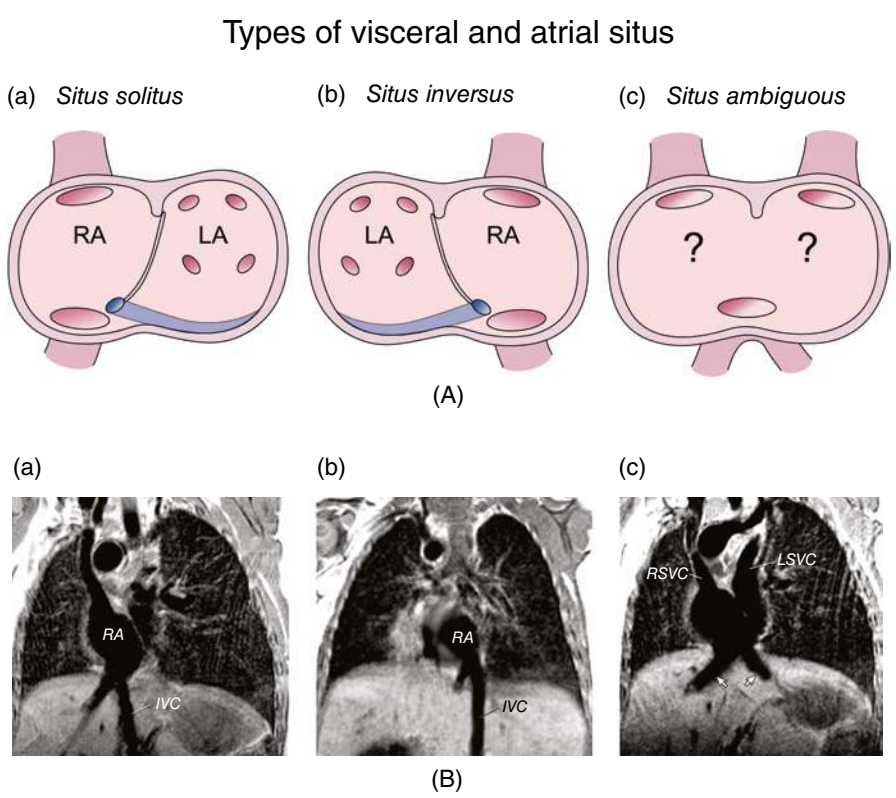


Figure 7.3 Atrial situs. (A): Graphic depiction of the various types of atrial situs (solitus, inversus, and ambiguous). In atrial situs solitus (a), the right-sided right atrium (RA) receives the caval veins and the orifice of the coronary sinus. The left-sided left atrium (LA) receives the pulmonary veins. In atrial situs inversus (b), the RA is left-sided and the LA is right-sided. In atrial situs ambiguous (c), the situs cannot be determined, as is frequently the case in heterotaxy syndrome. (B) Coronal plane spin echo magnetic resonance imaging in patients with heterotaxy syndrome and atrial situs solitus (a), atrial situs inversus (b), and atrial situs ambiguous (c). IVC, inferior vena cava; LSVC, left superior vena cava; RA, right atrium; RSVC, right superior vena cava. (Source: Geva [52]. Reproduced with permission of John Wiley & Sons.)

right and left atria. To evaluate the atrial situs, one must first morphologically identify the atrial chambers as described in the following section. The visceral anatomy may be used as an aid when defining atrial morphology because the atrial situs usually follows that of the viscera. Once the atrial chambers are identified, their arrangement (atrial situs) is defined (Figure 7.3). In *atrial situs solitus* (the normal arrangement), the morphologic right atrium is to the right of and anterior to the morphologic left atrium. In *atrial situs inversus*, the morphologic right atrium is to the left of and anterior to the morphologic left atrium. In *atrial situs ambiguous*, it is not feasible to clearly define the atrial sidedness.

The approach by Anderson classifies the atrial arrangements into four different types based on the morphology of the atrial appendages. Two of these variants fall within the category of *isomerism*, a term used to describe symmetry of a body structure or a mirror-image arrangement, in this case the atrial appendages. The four possible arrangements of the atrial chambers are *usual* (normally arranged or situs solitus), *mirror-imaged* (situs inversus), and – when both appendages have either right or left morphologic characteristics – the pathologic variants are referred to as either *right* or *left atrial isomerism*, respectively (Figure 7.4) [53–55]. Although the concept of isomerism as it relates to cardiac structures has been debated, the term is ubiquitous in day-to-day CHD parlance [56]. These atrial arrangements are associated with isomerism of the thoracic organs; *right isomerism* is usually found with asplenia, and *left isomerism* is found with polysplenia (Figure 7.5) [58].

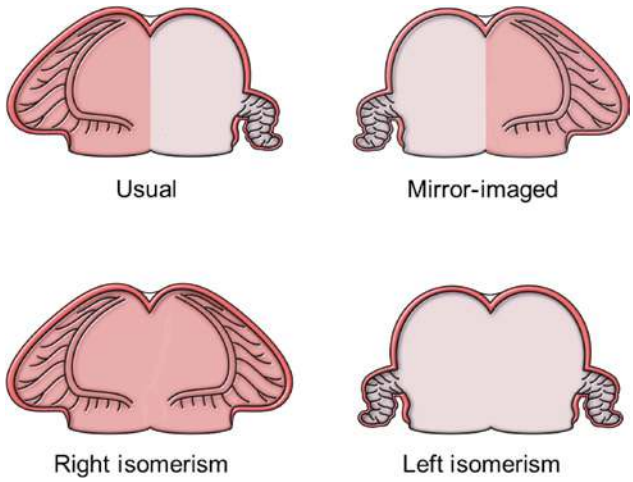


Figure 7.4 Atrial arrangements. The figure shows the four possible patterns of the atria (usual, mirror-imaged, right isomerism, and left isomerism) based on the morphology of the atrial appendages. (Source: Ms. Gemma Price. Reproduced with permission.)

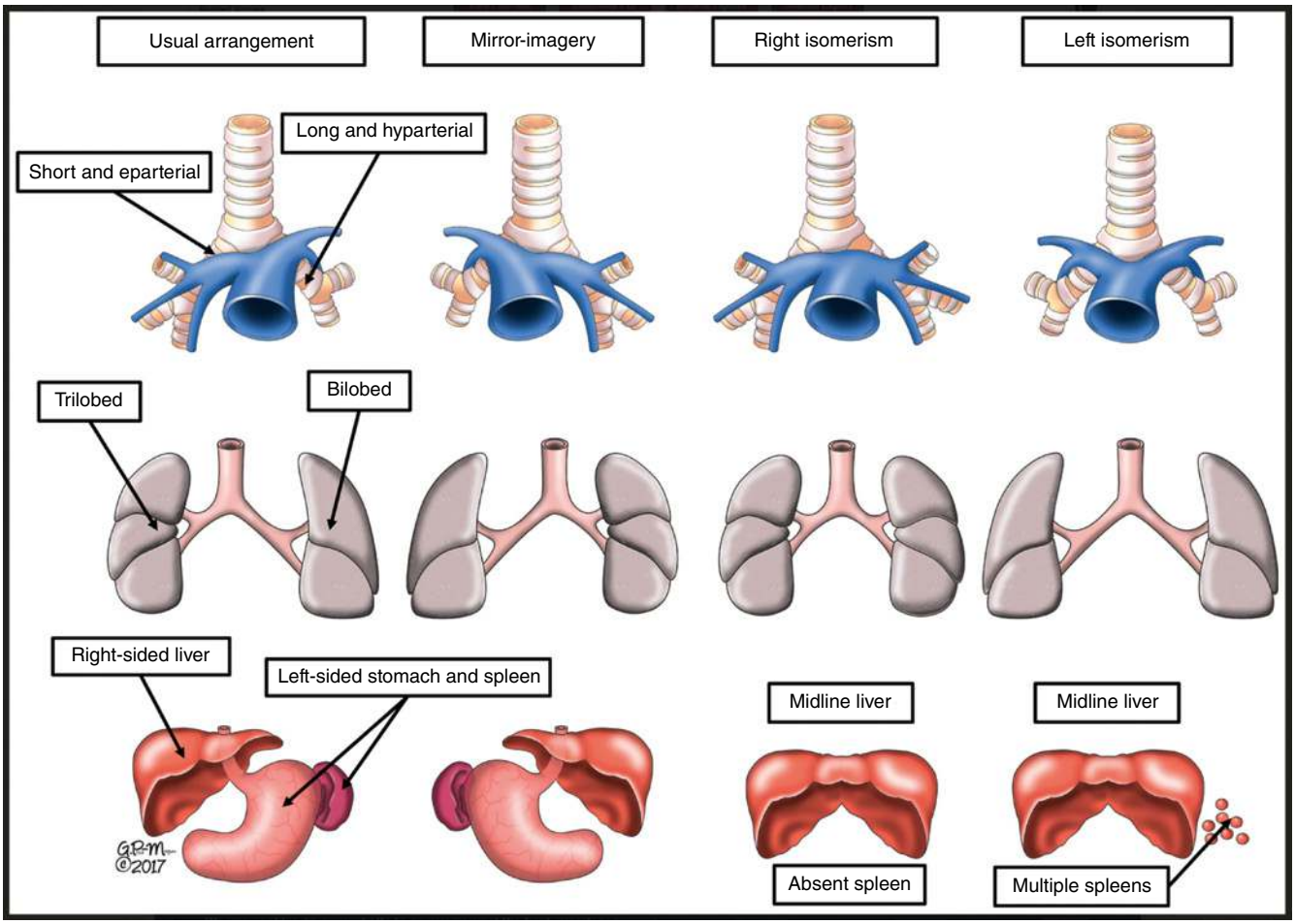


Figure 7.5 Variations of the bodily organs. The graphic displays the lateralized (left two columns) and isomeric (right two columns) arrangements of the bodily organs in the clinical settings. The *upper panels* show the bronchial morphology, and the relations of the bronchi to the pulmonary arteries. The *middle panels* show the pulmonary (lobar) morphology. The *lower panels* show the arrangement of the abdominal organs. (Source Anderson [57] / MDPI / CC BY 4.0.)

Because the atrial situs rarely differs from the visceral situs, as previously indicated, one may refer to this as the *visceroatrial situs*. In the Van Praagh shorthand notation [59], the types of visceroatrial situs are denoted as "S" for *situs solitus*, "I" for *situs inversus*, and "A" for *situs ambiguous*. Van Praagh has emphasized that the term situs ambiguous denotes that the visceroatrial situs is anatomically uncertain or indeterminate – as such, it is not a distinct or third type of situs, but rather a term used to indicate that the type of visceroatrial situs cannot be defined. As discussed under visceral situs ambiguous, this situs is usually seen in children with heterotaxy syndrome. In bilateral right-sidedness, or *right visceroatrial isomerism*, the atria, lungs, and bronchi are morphologically right-sided (Figure 7.5). Conversely, in bilateral left-sidedness, or *left visceroatrial isomerism*, the atria, lungs, and bronchi are morphologically left-sided. It must be emphasized that organ location, or situs, can differ, and discordance of the situs of different organs can exist (Figure 7.5).

KEY POINTS: VISCERAL AND ATRIAL SITUS

- The initial step of the sequential analysis involves assessing the visceral situs or anatomic relationships of the thoracoabdominal organs.
- The atrial situs rarely differs from the visceral situs.
- The three types of visceroatrial situs are situs soltitus (normal arrangement), situs inversus (mirror image arrangement), and situs ambiguous.
- In both situs solitus and situs inversus, there is asymmetry in the pattern of the abdominal/thoracic organs; by contrast, in situs ambiguous, a symmetric pattern is present with a tendency towards duplication of either right-sided or left-sided structures.
- Visceral situs ambiguous is usually associated with heterotaxy syndrome.

Great veins and atria

The structures most frequently considered under the subject heading of great veins are the vena cavae, pulmonary veins, and coronary sinus. *Systemic venous drainage* in the normal heart is via the superior vena cava (SVC) and IVC. These right-sided structures drain into the right atrium. The coronary sinus receives blood from the cardiac veins and empties into the floor of the right atrium, near the inferior aspect of the atrial septum and the orifice of the IVC. *Pulmonary venous drainage* is via the upper and lower right- and left-sided pulmonary veins. Venous variants (e.g., left SVC to the coronary sinus) or anomalies (e.g., interrupted IVC with azygous continuation or anomalous pulmonary venous connections) may co-exist with other defects in CHD; therefore, a complete anatomic examination includes an assessment of these structures to determine primarily their presence, patency, and sites of drainage.

Anatomic landmarks are the primary criteria used to identify and distinguish between the atrial chambers (Box 7.2). In a *morphologic right atrium*, the trabecular portion (pectinate muscles) extends from the crista terminalis to the base of the atrial appendage. A smooth sinusal portion is present between the crista terminalis and atrial septum. The septal aspect of the right atrium displays the superior and inferior limbic bands of the fossa ovale. The limbus is a thick muscular structure that can be used to identify the right atrium. The right atrial appendage has a broad base and a blunt tip (i.e. triangular shaped). In contrast, the *morphologic left atrium* has a smooth wall, and the left atrial appendage is narrow and elongated, or "finger-like." The septal aspect displays the thin valve of the foramen ovale. In the sequential segmental approach proposed by Anderson, the morphology of the atrial appendages is used as the foundation for identifying the atrial chambers.

The right atrium normally receives blood from the vena cavae and coronary sinus, and the left atrium receives blood from the pulmonary veins. However, as the systemic and pulmonary venous drainage may be variable and/or anomalous, as previously indicated, these criteria cannot be relied upon to definitively determine atrial morphology. Although the morphology of the atrial appendages is frequently used to define the atria and, therefore, the atrial situs, as noted, because the shape of the appendages may be subject to changes under various conditions, concern has been raised as to whether atrial appendage morphology is a reliable marker for identifying atrial structures and distinguishing between them [60].

The anatomic evaluation of the atria includes assessment of the interatrial septum and related areas for communications that may allow for atrial level shunting and the evaluation of pathology/variants that may be associated with structures such as the appendages and atrial cavities.

Box 7.2: Characteristics of the atrial chambers

Morphologic right atrium
- Broad-based (triangular-shaped) appendage
- Internal free wall has crista terminalis (also known as terminal crest), which is the boundary between the smooth-walled posterior aspect and the muscular anterior aspect of the chamber
- Extension of pectinate muscles toward the atrioventricular valve
- Septum secundum (limbus of the fossa ovalis)
- Normally receives the superior and inferior vena cavae and the coronary sinus

Morphologic left atrium
- Long and narrow (finger-like) appendage
- Smooth posterior surface receiving pulmonary veins, no crista terminalis
- Pectinate muscles contained within the appendage
- Septum primum (flap valve of the foramen ovale)
- Normally receives the pulmonary veins

KEY POINTS: GREAT VEINS AND ATRIA

- In the normal heart, systemic venous drainage is via the superior and inferior vena cavae into the right atrium and pulmonary venous drainage is via the right- and left-sided pulmonary veins into the left atrium.
- Anatomic landmarks are the primary criteria used to identify and distinguish between the morphologic right and left atria.
- Because systemic and pulmonary venous drainage can be variable and/or anomalous, these criteria cannot be relied upon to definitively determine atrial morphology.
- The anatomic evaluation of the atria includes assessment of the interatrial septum and the cavities to evaluate for pathology.

Ventricles and ventricular septum

An analysis of the ventricular segment includes determining the type of ventricular loop (topology or handedness of the ventricular mass; also referred to as describing the chirality) and the relative spatial relationship between the ventricles and the atria. *Ventricular looping*, as discussed in Chapter 6, can result in either D-loop (right-handed topology) or L-loop (left-handed topology) ventricles. In the normal D-loop heart, the morphologic right ventricle is right-handed (Figure 7.6A) and the morphologic left ventricle is left-handed, whereas in the L-loop heart, the morphologic right ventricle is left-handed (Figure 7.6B) and the morphologic left ventricle is right-handed. L-looping of the ventricles may also be referred to as ventricular inversion. The types of *ventricular situs* (loop or topology) have been described in the Van Praagh system [59] as follows: *solitus* or D-loop ventricles (D); *inverted* or L-loop ventricles (L); and *ambiguous* or X-loop ventricles, where X indicates unknown situs (looping cannot be determined).

The ventricles are defined by their anatomy and not by where they are spatially located. Ventricular morphology is used to identify the ventricles and, therefore, their location (Box 7.3). The morphologic *right ventricle* is triangular-shaped in nature and characterized by a trileaflet AV valve (tricuspid valve), consisting of septal, anterior, and posterior leaflets. The tricuspid valve inserts inferiorly onto the interventricular septum relative to the mitral valve and is termed septophilic because of its septal leaflet attachments to the interventricular septum. The densely trabeculated right ventricle consists of several papillary muscles. The pulmonary valve rests on a muscular infundibulum above the tricuspid valve. In contrast, the morphologic *left ventricle* is shaped similarly to a cone or bullet ellipse and is characterized by a bileaflet AV valve (mitral valve), consisting of anterior and posterior leaflets. There are no mitral valve attachments to the interventricular

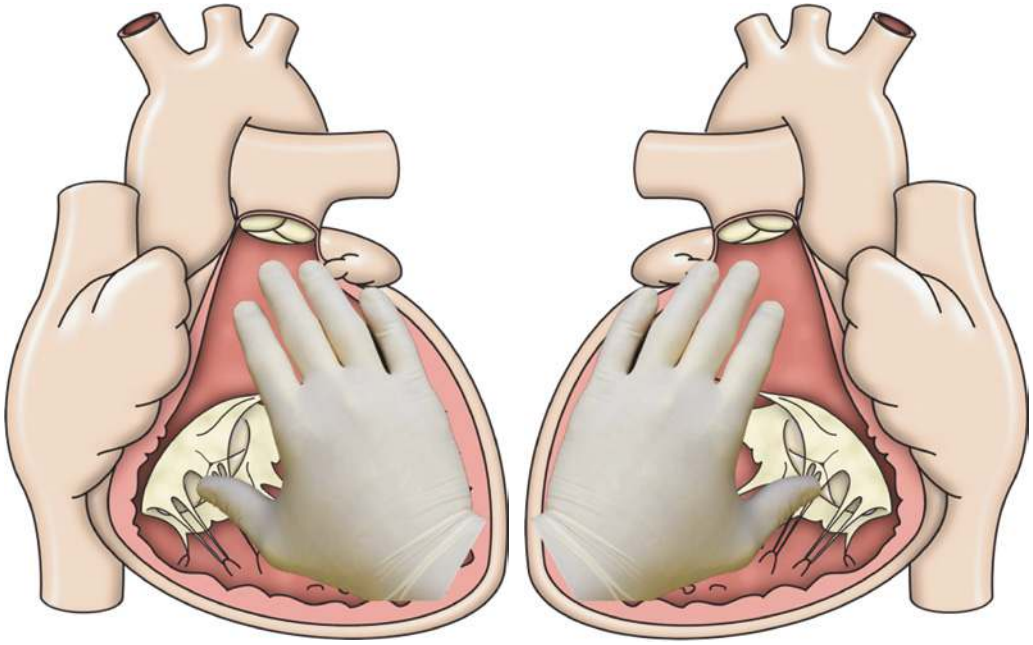


Figure 7.6 Ventricular topology. The figure shows how the position of the palmar surface of either the right hand (A) or the left hand (B) can be oriented over the septal aspect of the morphologic right ventricle (thumb over the ventricular inlet and fingers over the ventricular outlet), corresponding to D-loop (right-hand topology) or L-loop (left-hand topology). (Source: Ms. Gemma Price. Reproduced with permission.)

Box 7.3: Characteristics of the ventricular chambers

Morphologic right ventricle
- Trileaflet atrioventricular (tricuspid) valve with septal leaflet attachments to the interventricular septum (septophilic)
- Atrioventricular (tricuspid) valve more apically positioned on the interventricular septum when compared with the mitral valve
- Coarse muscular trabeculations at the apical portion
- Presence of moderator band and septomarginal trabeculation (characteristic muscle band on the septal aspect)
- Tricuspid valve is separated from the pulmonary valve by the crista supraventricularis (supraventricular crest) or infundibulum
- Chamber shaped like a triangle

Morphologic left ventricle
- Bileaflet atrioventricular (mitral) valve without septal attachments (septophobic)
- Atrioventricular (mitral) valve with superior position on the interventricular septum, as compared with the tricuspid valve
- Smooth muscular trabeculations at the apical portion
- Absence of moderator band, presence of paired papillary muscles
- Mitral valve in fibrous continuity to aortic valve (infundibulum absent)
- Chamber shaped like a cone

septum; therefore, the valve is referred to as septophobic. The left ventricle has a smooth wall (fine trabeculations) and contains two prominent papillary muscles. The anterolateral and posteromedial papillary muscles have chordal attachments supporting the anterior and posterior mitral valve leaflets. The aortic and mitral valves share fibrous continuity in the normal heart.

The *ventricular septum* separates the right and left ventricles. A ventricular septal defect represents an opening or gap in the ventricular septum. This is one of the most common intracardiac defects and also the most common type of CHD requiring surgery. These defects vary in size, shape, and location and can occur anywhere in the ventricular septum as single or multiple entities. They are classified into various types depending on their location (Figure 7.7), also refer to Chapter 6 [24]. The evaluation of the ventricular septum is complicated by the fact that it is not a straight wall that divides the ventricles but rather a three-dimensional structure that includes the membranous, muscular (also known as trabecular), infundibular, inlet, and AV segments. Characterizing defects in the ventricular septum thus requires a detailed, systematic examination as they can be circumscribed to a specific area or span various regions.

KEY POINTS: VENTRICLES AND VENTRICULAR SEPTUM

- Analysis of the ventricular segment involves determining the type of ventricular loop and the relative spatial relationship between the ventricles and the atria.
- Ventricular looping can result in D-loop (right-handed) or L-loop (left-handed) ventricular topology.
- The ventricles are defined by their anatomy and not by where they are spatially located; ventricular morphology is used to identify the ventricles and, therefore, their location.
- The ventricular septum is a three-dimensional structure comprising various segments, implying complexity in its evaluation and in examining interventricular communications.

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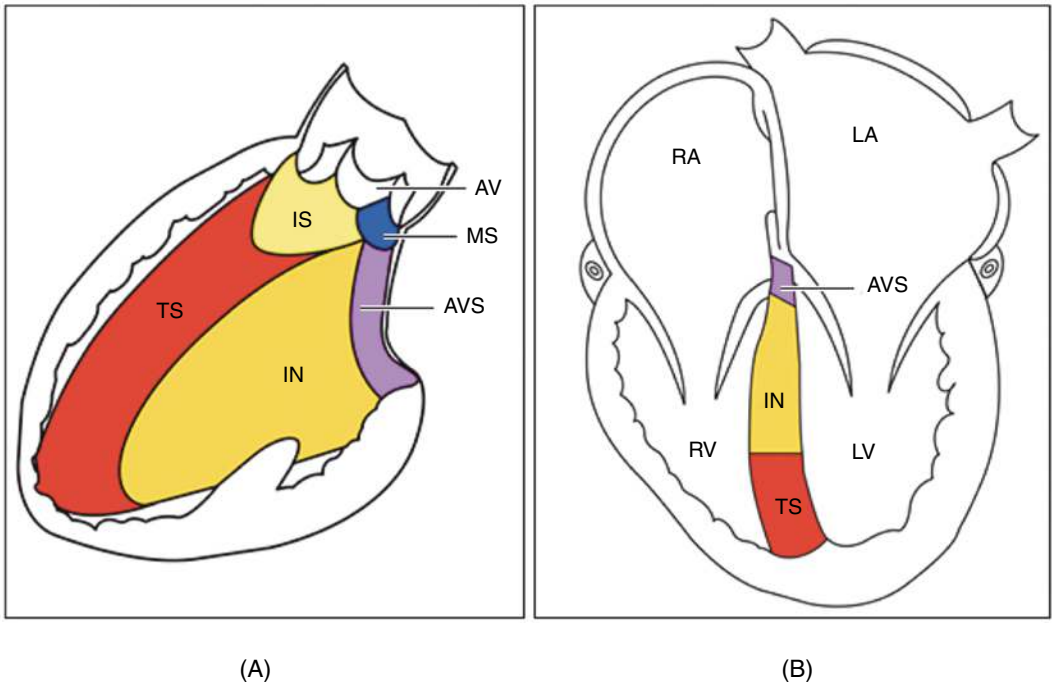


Figure 7.7 Segments of the ventricular septum. Diagrammatic illustration of the various segments of the ventricular septum as viewed from the left ventricle (A) and along the length of interventricular septum (B): membranous (MS), infundibular (IS), trabecular (TS), inlet (IS), and atrioventricular (AVS) septum. AV, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Source: Ammash [61]. Reproduced with permission of John Wiley & Sons.)

Atrioventricular junction

The AV junction, or AV canal, consists of the AV valves and AV septum.

Atrioventricular valves

An important aspect of the evaluation for CHD is an assessment of the AV valves (tricuspid and mitral valves). This analysis includes determining valvular patency, leaflet morphology (size, number, and commissures), annular dimensions and orifice shape, in addition to evaluating chordal structures and papillary muscles that comprise the support apparatus. Other features of the AV valves that are of interest include the point of septal insertion at the annulus and the presence/absence of chordal attachments to the ventricular septum. As indicated previously, these features facilitate the morphologic identification of the ventricles because the AV valves are *almost always* associated with their respective ventricles (i.e., the tricuspid valve with the right ventricle and the mitral valve with the left ventricle).

Atrioventricular connections

To ascertain the connection between the atria and ventricles, or the sequence of these structures, it is necessary to first fully analyze each of these segments and identify the chambers. Several AV connections/alignments may be possible, as depicted in Figure 7.8. The AV connection can either be biventricular or univentricular. Biventricular connections can be classified into either concordant or discordant. A *concordant AV connection* implies that the normal anatomic relationship exists, meaning the morphologic right atrium connects to the morphologic right ventricle and the morphologic left atrium connects to the morphologic left ventricle. In the case of a *discordant* AV *connection*, the morphologic right atrium opens into the morphologic left ventricle and the morphologic left atrium opens into the morphologic right ventricle [48]. Examples of cardiac defects in which the AV relationship is discordant include corrected transposition (characterized by both AV and VA discordance) and isolated ventricular inversion (AV discordance and VA concordance). The term univentricular AV connection is used when only one ventricle is connected to the atrial chamber. In children with a single ventricle, the AV relationship may differ.

The presence of concordant or discordant AV connections is independent of ventricular position, meaning that either connection can be seen in situs solitus or situs inversus. In the sequential analysis, the AV connection/alignment can also be described as *common* (e.g., common AV valve), *double inlet* (double-inlet left ventricle), *absent* (AV valve atresia), *overriding* (when the annulus of the valve sits above portions of both ventricles (or ventricle and outlet chamber; e.g. double outlet right atrium), or *straddling* (where parts of the tensor apparatus of the valve attach on both sides of the septum; e.g., straddling mitral valve) (Figure 7.8).

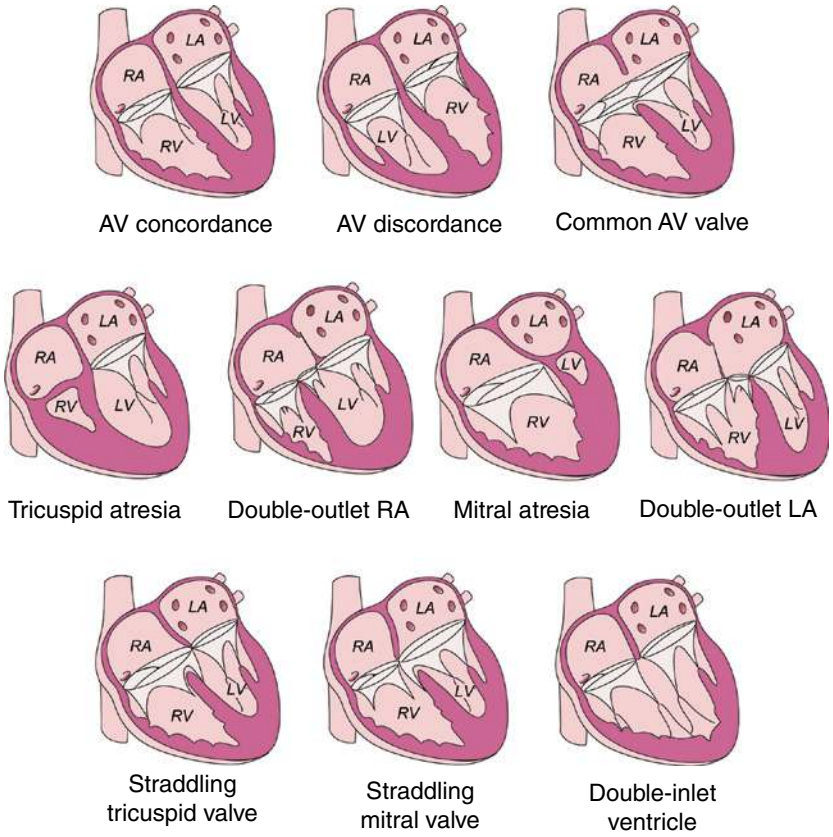


Figure 7.8 Atrioventricular alignments and connections. Diagrammatic representation of potential atrioventricular (AV) alignments and connections. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Source: Geva [52]. Reproduced with permission of John Wiley & Sons.)

KEY POINTS: ATRIOVENTRICULAR JUNCTION

- An important aspect of morphologic evaluation in CHD is the assessment of the AV valves.
- The AV valves are almost always associated with their respective ventricles.
- To determine the AV connections or sequence of anatomic structures, each of the chambers should be identified first.
- The AV connection can be either biventricular or univentricular; biventricular connections can be classified into either concordant or discordant.
- The presence of concordant or discordant AV connections is independent of ventricular position.

Ventriculoarterial junction

The VA junction (infundibulum/conus arteriosus) is the cardiac segment that connects the ventricles to the great arteries. Various aspects of this connection should be considered during a morphologic evaluation, as explained in the following sections.

Conal or infundibular anatomy

The distal region of the conus arteriosus, identified by the muscular infundibulum, is normally found immediately underneath the pulmonary valve, separating the tricuspid valve from the pulmonary valve. In contrast, there is fibrous continuity between the mitral and aortic valves (mitro-aortic continuity), and no intervening muscular tissue is present in the normal heart. An important element to include when describing cardiac anatomy is the morphology of the infundibulum, or outlet portion of the ventricles, which occurs essentially in four different anatomic types. These are depicted in Figure 7.9. In the normal heart, as previously noted, the infundibulum is in the subpulmonary location. Alternatively, the muscular infundibulum can be in the subaortic location (e.g. in D-transposition of the great arteries), bilateral (e.g. in a double-outlet right ventricle), or deficient/absent (e.g. in the rare case of a double-outlet left ventricle).

Semilunar valves

The semilunar or arterial valves are the connecting structures between the ventricular masses and great arteries. The valvular components usually described during an anatomic evaluation include the annulus, cusps, commissures, sinuses, sinotubular junction, and supporting ventricular musculature. Other important elements to assess as part of the anatomic examination include

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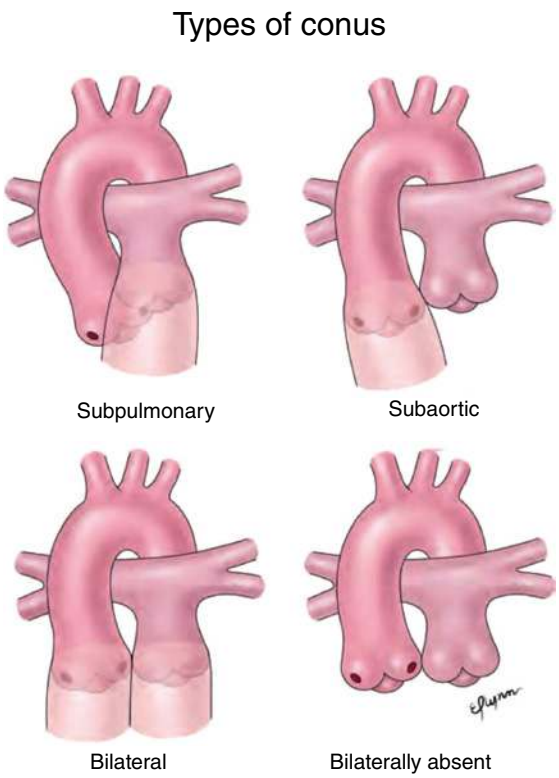


Figure 7.9 Types of conus (infundibulum). The location of the muscular infundibulum categorizes the conal anatomy into four basic types: subpulmonary conus, as found in the normal heart; subaortic conus, as often found in transposition of the great arteries; bilateral conus (in subpulmonary and aortic locations), as usually identified in patients with double-outlet right ventricle; and bilaterally absent (rare), as may be found in some patients with double-outlet left ventricle. (Source: Geva [52]. Reproduced with permission of John Wiley & Sons.)

valvular patency, degree of hypoplasia (when present), and potentially related abnormalities.

Ventriculoarterial connections

To determine the type of VA connection, one must examine the outflow tracts to define the ventricular origin of the great arteries and the relationship between the semilunar valves and the ventricles. There are no intrinsic features that distinguish between the great arteries, and therefore the branching pattern of the arterial trunks is used to establish their identity (see the sections that follow) [33]. Four basic VA connections are recognized: concordant, discordant, double-outlet, and single-outlet.

In *VA concordance* (connection to an appropriate ventricle), the pulmonary artery arises from the right ventricle and the aorta arises from the left ventricle. This connection has been considered normal in solitus normal or inverted normal. This relationship is in contrast to a *discordant VA connection* (connection to an inappropriate ventricle), in which the pulmonary artery arises from the left ventricle and the aorta arises from the right ventricle, as is most commonly seen in transposition of the great arteries (e.g. D-transposition, L-transposition, or A-transposition). Other connection types include double outlet and single outlet, as shown in Figure 7.10. The term *double outlet* is used when both great arteries originate from one ventricle or when one vessel arises from the ventricle and the second one overrides the septum by over 50% (e.g. double-outlet right ventricle). Another criterion used to identify this type of connection is a lack of fibrous continuity between the mitral valve and adjacent semilunar valve. A *single-outlet connection* refers to a solitary great artery arising from the ventricle, the other being atretic (e.g. pulmonary atresia and aortic atresia) or a common arterial trunk (e.g. truncus arteriosus).

KEY POINTS: VENTRICULOARTERIAL JUNCTION

- A muscular infundibulum (conus) normally separates the tricuspid and pulmonary valves, in contrast to the presence of fibrous continuity between the mitral and aortic valves.
- Examination of the semilunar valves is an important aspect of CHD evaluation.
- Determination of the type of VA connection requires definition of the ventricular origin of the great arteries and the relationship between the semilunar valves and the ventricles.
- No intrinsic feature distinguishes between the great arteries, and therefore the branching pattern of the arterial trunks is used to establish their identity.
- The four basic VA connections are concordant, discordant, double outlet, and single outlet.

Great arteries and their relationships

As described in detail in Chapter 6, the developmental changes that occur in the conotruncal region during embryonic life result in a spiral or criss–cross relationship between the great arteries in the normal heart. In individuals with normally related great arteries, the main pulmonary artery is anterior to the aorta and courses leftwards before bifurcating into the left and right branches, whereas the aorta is posterior with respect to the main pulmonary artery and courses rightwards, giving rise to the coronary arteries, the vessels of the head and neck, and most systemic arteries. In addition, the pulmonary valve sits anterior to and leftwards of the aortic valve. This great artery/semilunar valve relationship may be altered, resulting in a parallel (i.e. side-by-side) relationship and other abnormal spatial orientations. As part of a complete examination, the spatial relations between the great arteries and the semilunar valves (anterior-posterior and right–left position) are usually described. The Van Praagh system [59] defines the types of great arterial situs (i.e., spatial relations of the great arteries) as follows:

- *Solitus* (aortic valve right-sided relative to pulmonary valve) – normally related great arteries (S), or D-transposition/malposition (D)
- *Inversus* (aortic valve left-sided relative to the pulmonary valve) – inverted (mirror image), normally related great arteries (I), or L-transposition/malposition (L)
- *Ambiguous* (right-left location of the aortic valve, directly anterior to the pulmonary valve, is equivocal, meaning neither right or left) – A-transposition/malposition (A).

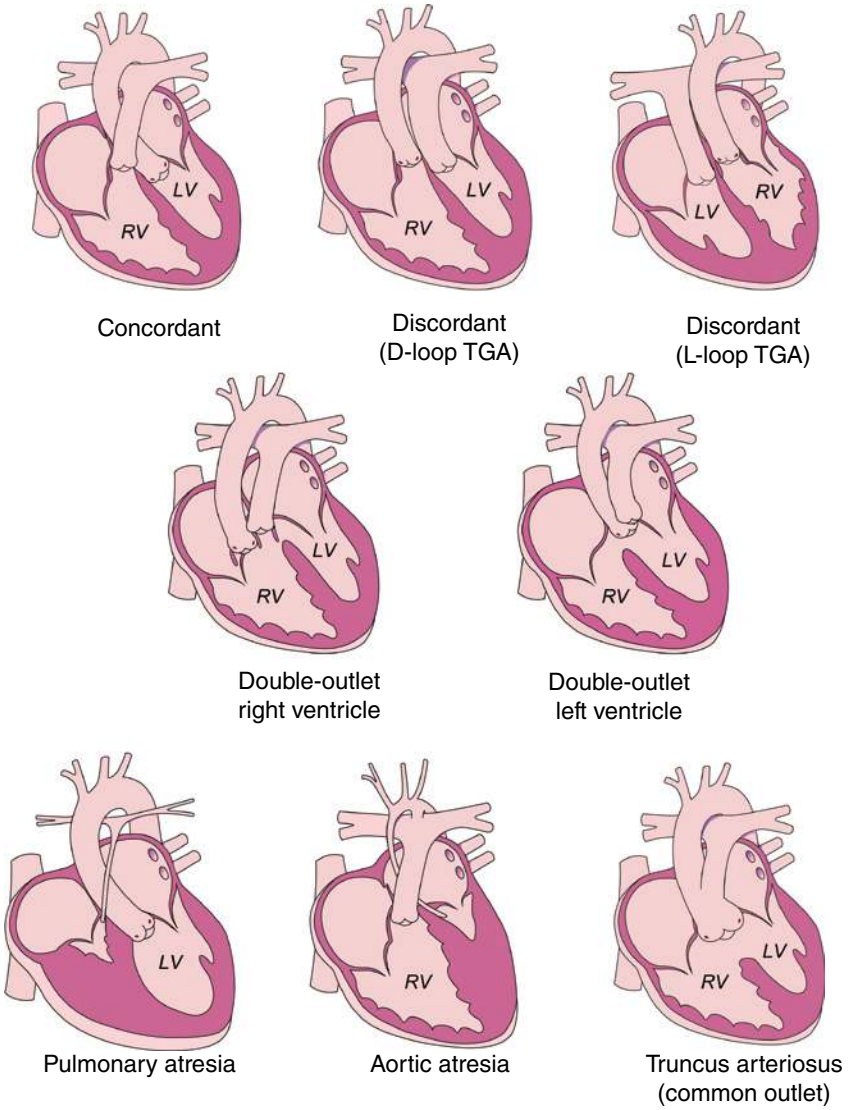


Figure 7.10 Ventriculoarterial alignments and connections. Diagrammatic representation of potential ventriculoarterial connections/alignments. D-TGA, D-loop transposition of the great arteries; L-TGA, L-loop transposition of the great arteries; LV, left ventricle; RV, right ventricle. (Source: Geva [52]. Reproduced with permission of John Wiley & Sons.)

KEY POINTS: GREAT ARTERIES AND THEIR RELATIONSHIPS

- An important component of the morphologic examination in CHD is the description of the spatial relationships between the great arteries and the semilunar valves.
- In the normal heart, there is a spiral or criss–cross relationship between the great arteries; this relationship may be altered, resulting in a parallel relationship and other abnormal spatial orientations.
- The great arterial situs in the Van Praagh system is defined as solitus, inversus, or ambiguous.

Branch pulmonary arteries and ductus arteriosus

In the normal heart, the main pulmonary artery emerges from the morphologic right ventricle and courses to the left of the ascending aorta. The main pulmonary artery bifurcates into right and left branches. The course of each branch is distinct: the right pulmonary artery originates almost in perpendicular fashion from the main pulmonary artery and travels beneath the aortic arch and posterior to the SVC, whereas the left pulmonary artery continues in a smooth arch-like fashion from the pulmonary confluence over the left mainstem bronchus. As indicated previously, the thoracic organs are asymmetrical, which accounts for the different branching patterns of the right and left pulmonary arteries and their relationships to the tracheobronchial tree. These differences facilitate the determination of lung morphology and sidedness.

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The ductus arteriosus is a vascular channel that serves as an essential communication between the pulmonary artery and the descending aorta during fetal life. In most cases, the ductus arteriosus originates from the postero-superior aspect of the junction between the main and left pulmonary arteries and inserts into the anterolateral or ventral aspect of the descending thoracic aorta, just distal to the takeoff of the left subclavian artery. However, the site of origin and the course of the ductus arteriosus can be variable, which is most likely to be the case in complex cardiac pathology. This vascular channel should spontaneously close soon after birth. If it fails to close, a persistent connection between the great arteries is present, which allows for shunting (i.e. patent ductus arteriosus). In certain types of congenital malformations, patency of this communication is essential for either pulmonary or systemic blood flow and, therefore, for survival.

Aortic arch

The aortic arch can be divided into three components: the ascending, transverse, and descending portions. The origin of the three arch vessels (brachiocephalic, carotid, and subclavian arteries) are routinely determined as part of the aortic arch evaluation. An examination of these structures should focus on assessing vessel patency and size, aortic arch position, arch sidedness, and branching pattern (i.e. origin of the head and neck vessels). Vascular anomalies or variants should also be identified. Aortic arch sidedness (left or right) is defined by which mainstem bronchus is crossed by the aortic arch or, likewise, by the position of the aortic arch relative to the trachea. The aortic arch is normally left-sided, and the aortic arch vessels branch in sequence into the right innominate or brachiocephalic (which divides into the right subclavian and right common carotid arteries), left common carotid, and left subclavian arteries. Of note is that arch sidedness is not incorporated into the sequential segmental approach but nevertheless represents an important aspect of anatomic evaluation of the cardiovascular system.

KEY POINTS: BRANCH PULMONARY ARTERIES, DUCTUS ARTERIOSUS, AND AORTIC ARCH

- The main pulmonary artery arises anteriorly from the morphologic right ventricle and courses to the left of the ascending aorta bifurcating into its right and left branches.
- The ductus arteriosus is an essential communication between the great arteries during fetal life. It usually originates at the junction between the main and left pulmonary arteries and inserts into the ventral aspect of the descending thoracic aorta, just distal to the origin of the left subclavian artery.
- Important aspects of the aortic arch examination include determination of sidedness (normally left-sided) and branching pattern.
- Vascular anomalies or variants are also usually characterized.

Coronary arteries

An examination of the major epicardial coronary arteries, including their origin, proximal course, and branching pattern, is an essential component of the anatomic evaluation for CHD. Normally, two major coronary arteries (the right and left main) arise from the aortic root from their respective sinuses of Valsalva facing the main pulmonary artery. The left main coronary artery bifurcates into the left anterior descending and circumflex coronary arteries. In the clinical setting, advanced imaging modalities are required to assess the more distal branches of the main vessels (e.g., diagonals, marginals, and septal perforators) and the dominant coronary system (determined by the origin of the posterior descending branch). The right and circumflex coronary arteries normally course along the AV groove and near the AV valves. The left anterior descending coronary artery travels along the interventricular septum. Variations from these patterns or abnormalities in the origin, course, or branching of the coronary arteries may be recognized clinically as incidental findings, and they can be found in isolation or in association with other cardiac defects. In some instances, variable coronary artery patterns can influence the type of surgical repair (e.g. in tetralogy of Fallot the left anterior descending can arise from the right coronary artery and cross the right ventricular outflow tract, thereby precluding placement of a patch).

Description of associated malformations

In addition to the detailed examination described in previous sections, any morphologic approach for evaluating the cardiovascular system and major cardiac defects requires an accurate and detailed assessment of any co-existing malformations as part of a comprehensive anatomic analysis for CHD.

Summary

Caring for patients with structural malformations of the cardiovascular system is an important aspect of anesthesia practice and the main focus for those who specialize in pediatric cardiac anesthesiology. The variable spectrum of CHD ranging widely from relatively simple defects to complex ones, along with the different terminology, nomenclature and classification systems utilized in clinical practice, has created confusion and added to the already significant challenges. However, it is important for the practicing anesthesiologist who cares for these patients to understand the various nomenclature systems used to describe congenital cardiac pathology and not only be comfortable but well versed in these. Efforts in the medical community to establish a uniform naming system for pediatric and CHD have made significant strides in the last two decades. These will continue to incorporate the perspectives of many different disciplines and specialties to further refine this work while attempting to overcome many of the ongoing challenges.

To provide optimal care for patients with congenital cardiovascular malformations, one must have a solid understanding of the anatomic abnormalities, the altered pathophysiology, and the associated hemodynamic consequences

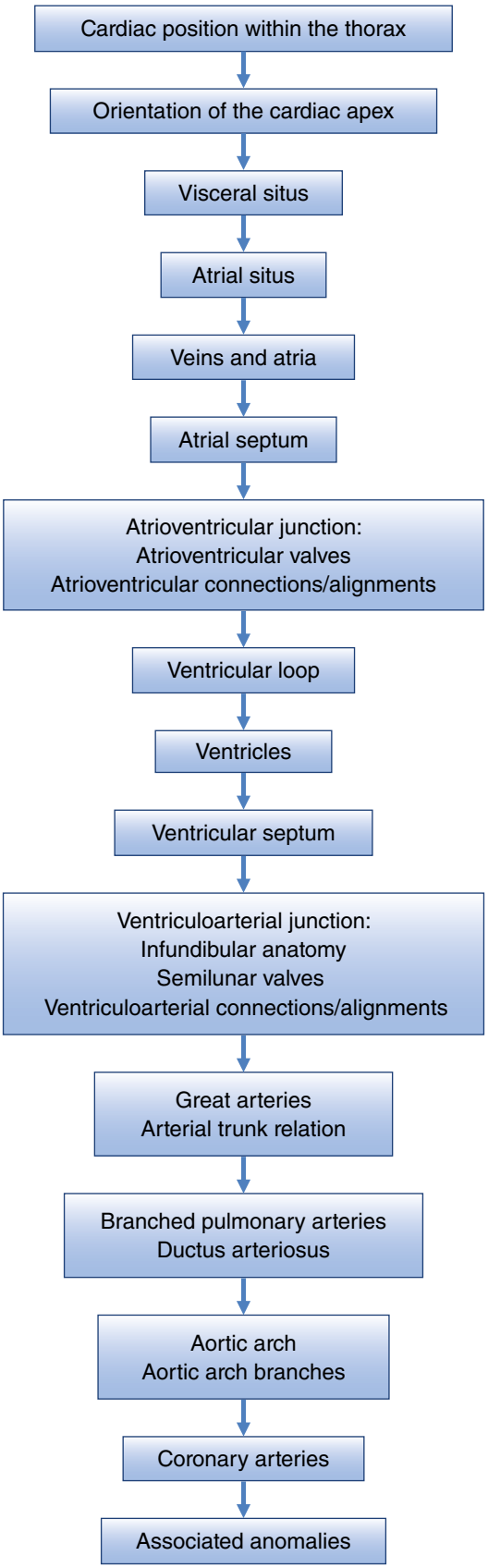


Figure 7.11 Segmental evaluation of congenital heart disease. Illustration of the steps involved in the segmental approach to diagnosis of congenital heart disease. (Source: Geva [52]. Reproduced with permission of John Wiley & Sons.)

of the disease. Important requirements in this regard include having a solid framework concerning the steps involved in the segmental anatomic evaluation of the heart as described in this chapter and summarized in Figure 7.11.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

7 Franklin RC, Jacobs JP, Krogmann ON, et al. Nomenclature for congenital and paediatric cardiac disease: historical perspectives and The International Pediatric and Congenital Cardiac Code. Cardiol Young 2008;18(Suppl 2):70–80. Important article describing the efforts of the cardiothoracic surgical groups over the years to establish a common diagnostic and therapeutic nomenclature in pediatric cardiac disease.

23 Franklin RCG, Béland MJ, Colan SD et al. Nomenclature for congenital and paediatric cardiac disease: the International Paediatric and Congenital Cardiac Code (IPCCC) and the Eleventh Iteration of the International Classification of Diseases (ICD-11). Cardiol Young 2017;27:1872–938. Excellent article describing linking efforts between the International Nomenclature Society and the World Health Organization to obtain a globally accepted nomenclature tree for CHD within the 11th iteration of the International Classification of Diseases.

33 Anderson RH, Shirali G. Sequential segmental analysis. Ann Pediatr Cardiol 2009;2:24–35. Excellent review that outlines the steps involved in the sequential segmental analysis to categorize congenitally malformed hearts (Dr. Anderson's approach).

47 Anderson RH. Has the congenitally malformed heart changed its face? Journey from understanding morphology to surgical cure in congenital heart disease. Circ Res 2017;120:901–3. Outstanding contemporary viewpoint from Dr. Robert H. Anderson addressing how our understanding of CHD has changed over time and differences in nomenclature of cardiac anomalies that can now be resolved by recent advances in our knowledge of cardiac development and genetics.

59 Van Praagh R. Terminology of congenital heart disease. Glossary and commentary. Circulation 1977;56:139–43. Excellent article that provides a comprehensive explanation of the terminology used in congenital heart disease and describes Dr. Van Praagh's short-hand notation.

CHAPTER 8

Genetic Syndromes and Associations in Congenital Heart Disease

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Introduction

Approximately 20–30% of patients with congenital heart disease (CHD) also have a genetic syndrome or association comprised of cardiac and extracardiac features [1]. Therefore, patients with genetic syndromes or associations are seen disproportionately in locations where care is provided to patients with CHD. The presence of a syndrome or genetic abnormality is a risk factor for perioperative morbidity/mortality for congenital heart surgery [2], and noncardiac and genetic abnormalities can be associated with additional risk factors such as prematurity and weight <2.5 kg [1]. Patel et al. analyzed the Society of Thoracic Surgeons Congenital Heart Surgery Database and reported on the overall prevalence of noncardiac congenital anatomic abnormalities, genetic abnormalities, and syndromes in neonates undergoing congenital heart surgery of 18.8%. The congenital heart lesions with the highest incidence of a noncardiac anomaly, genetic abnormality, or syndrome were an atrioventricular septal defect, interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot. The most common genetic abnormalities were heterotaxy syndrome, 22q11 deletion, trisomy 21, and Turner syndrome [3]. The presence of a genetic syndrome or abnormality clearly makes a difference in in-hospital mortality in hypoplastic left heart syndrome (HLHS) and in conotruncal anomalies. The reported in-hospital mortality for HLHS in patients with a genetic abnormality is 26.7% compared with 19.8% in patients without a genetic abnormality [4]. Michielon et al. report that 22q11 deletion and Trisomy 21 are not risk factors for mortality after repair of conotruncal anomalies, but VACTERL association was associated with a higher risk of mortality [5]. In addition to the well-known chromosomal disorders and genetic syndromic associations in CHD, newer genetic analysis tools such as whole-exome sequencing (see below under Genetic Testing) are discovering many new, complex gene variants that are associated with CHD, and so the knowledge of the genetic basis of CHD is expanding and it is likely that an even higher percentage of CHD patients have variants that can explain both the cardiac disease and extracardiac manifestations [6]. Certain genetic syndromes are known to carry an increased anesthetic risk. An understanding of the genetic basis, manifestations, and impact of perioperative management in patients with these syndromes and associations is important for risk stratification, counseling, decision-making, and mitigation of anesthetic and perioperative risk [1].

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Historically, cardiac repair was not offered for patients with some genetic syndromes, including Trisomy 21. In the present day, cardiac repair is often expected, and cardiac transplantation has been performed in patients with Trisomy 21. This change in the pattern of care has increased the life expectancy of patients with Trisomy 21, and patients with Eisenmenger syndrome and other sequelae of long-standing unrepaired cardiac disease rarely present for anesthetic care in the modern era in developed countries. This same evolution is now being seen with other syndromes with Trisomy 21 being the model for nonbiased treatment of CHD [7]. As operative management becomes more common, it is important to tailor perioperative management to optimize outcomes. Genetic-specific treatment and management protocols have been suggested to reduce perioperative morbidity and mortality [7].

In this chapter, common genetic syndromes and associations in patients with CHD are explored including the genetic defect and inheritance, cardiac and noncardiac manifestations, along with some anesthetic considerations and risk mitigation, and the effect of the syndrome on surgical morbidity and mortality. Detailed approaches to anesthetic and surgical management of the specific cardiac lesions are contained in the corresponding chapters in this textbook. Patients with congenital heart disease and genetic and dysmorphic associations present complex diagnostic and management decisions because of multiorgan disease, and many of these patients have neurodevelopmental disabilities, and some have limited life expectancy. Because of these issues, approaches to genetic testing, ethical considerations, and palliative care are also discussed.

Chromosome 22q11 deletion syndrome

Velocardiofacial syndrome (VCFS), which is also termed DiGeorge syndrome or sequence, 22Q11 deletion syndrome, CATCH 22, and conotruncal anomalies face syndrome, has a broad spectrum of phenotypic variation with more than 180 clinical features. VCFS is one of the most common multiple anomaly syndromes, estimated to occur in approximately 1 : 2,000 live births. VCFS is inherited as an autosomal dominant disorder caused by a microdeletion at chromosome 22q11.2 [8]. The phenotype is extremely heterogeneous, and there is no single clinical feature present in all cases, therefore the diagnosis is established by the chromosome defect itself. Congenital heart disease is present in 70% of cases and comprises a high proportion of all conotruncal anomalies, including more than 50% of cases of interrupted aortic arch, over 15% of patients with tetralogy of Fallot, about 50% of truncus arteriosus patients, and about one third of posteriorly malaligned ventricular septal defects. Hemizygosity of the gene TBX1 is responsible for cardiac defects. Other defects commonly present are cleft palate, usually submucous clefts. Facial anomalies are often associated and include high arched palate, low set ears, and occasionally, varying degrees of micrognathia (Figure 8.1) [8]. Other important features present in a variable percentage of patients are partial hypoparathyroidism causing neonatal hypocalcemia, and relative immunodeficiency from abnormal lymphocyte function. Neurodevelopmental disability is common in VCFS, although in some patients intelligence is normal. The average mean full-scale IQ is 70–75, with about 55% having an IQ range of 70–100; 45% having an IQ range of 55–70, and a few patients have moderate to severe disability [9]. Individuals with VCFS are at an increased risk for developing a number of neuropsychiatric disorders which include attention deficit with hyperactivity disorder, anxiety and mood disorders, autism spectrum disorder, psychotic disorders, and schizophrenia. Patients with the cardiac diseases noted above should be tested for the 22q11.2 deletion syndrome using fluorescence-in-situ hybridization (FISH) or chromosomal microarray (CMA), and other multisystem involvement should be assessed as well, especially hypocalcemia and immune dysfunction leading to increased infection risk, as these may affect anesthetic management. In patients with simpler forms of CHD and VCFS, i.e. tetralogy of Fallot, VSD, and simple truncus arteriosus, surgical outcomes are the same as patients without a chromosome defect. However, in the interrupted aortic arch, surgical outcomes are poorer with the 22q11.2 deletion. Finally, the later neurodevelopmental outcomes at one year or more after cardiac surgery are worse overall with 22q11.2 deletion [10]. In spite of the known mild craniofacial anomalies in this syndrome, airway management and tracheal intubation is most often not problematic.



Figure 8.1 Facial features of the velocardiofacial syndrome. Note the small low-set posteriorly rotated ears and slight retrognathia; the patient also has a high arched palate with submucous cleft. (Source: Shprintzen [53]. Reproduced with permission from John Wiley & Sons.)

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Trisomy 21

The most common genetic syndrome, Down syndrome (DS) affects about 1/700 live births [11]. Resulting from an additional 21st chromosome, diagnosis often occurs *in utero* with abnormal levels of maternal serum markers (alpha-fetoprotein, human chorionic gonadotropin, pregnancy-associated plasma protein-A, and inhibin A), as well as increased nuchal translucency and a shortened nasal bone on ultrasound in the first trimester [12, 13]. Postnatal diagnosis is based on a physical exam and FISH to confirm the presence of an extra chromosome 21 (3). Children with DS are typically hypotonic with highly mobile joints and distinctive physical features, including a small head with a short neck, macroglossia, palpebral fissures, broad short hands with a single palmar crease, and Brushfield's spots on the iris (3) (Figure 8.2) [14, 15]. They typically have short stature and obesity is prevalent with increasing age. Prematurity and low birth weight (<2,500 g) occur more frequently compared to the general population [11, 14]. The presence of a flat nasal bridge, macroglossia, and a smaller hypopharynx with decreased muscle tone, and increased tonsillar and adenoid hypertrophy lead to airway obstruction and obstructive sleep apnea (OSA). In addition, children with DS may have smaller airways with an increased incidence of subglottic stenosis, as well as lower airway disease from reduced airway branching units due to a reduced number of alveolar acini [14]. As many as 8% of children with DS have hypothyroidism which should be screened for annually. Hematologic disturbances including neutrophilia, polycythemia, and thrombocytopenia are common in the newborn period and, in addition, 10% of neonates with DS will have a transient myeloproliferative disorder, also known as transient megakaryoblastic leukemia. Cervical spine abnormalities such as atlantoaxial instability are estimated to occur in 15% of children with DS.



Figure 8.2 Typical facial features of Down syndrome. Note the epicanthal folds, upslanting palpebral fissures, flat facial profile, and relatively large tongue. (Source: Davidson [12]. Reproduced with permission from Elsevier.)

Greater than 40% of children with DS are born with congenital heart disease with atrioventricular septal defect (AVSD), ventricular septal defect (particularly a canal type VSD), tetralogy of Fallot, and patent ductus arteriosus being most common. Racial differences exist in which black children with DS have a much higher incidence of AVSD. Despite a higher prevalence of prematurity and comorbidities than children without DS, no significant difference has been found in survival after congenital cardiac surgery in children with DS [16–18]. Children with DS who undergo mask induction with sevoflurane are known to have an increased risk of bradycardia. In a study of 209 children with DS, 57% experienced significant bradycardia unrelated to the presence of congenital heart disease [11, 19]. While the bradycardia is typically self-limited, cases of cardiovascular collapse have been documented [20].

Down syndrome patients are known to be at higher risk of developing pulmonary hypertension (PH), especially in the neonatal period. While the lifetime incidence of PH in children with DS remains unknown, one large, retrospective study of children with DS reported an incidence of PH as high as 28% [21]. Prematurity and LBW increase the risk of the development of bronchopulmonary dysplasia-related PH. Chronic airway obstruction and hypoxia result in increased arteriolar hypertrophy of the pulmonary vasculature which can develop into pulmonary hypertension. Cardiac defects such as AVSD and VSD with a large left to right shunt lead to increased pulmonary blood flow which can further increase the pulmonary vascular resistance. These factors in addition to pulmonary hypoplasia and intrinsic endothelial dysfunction lead to an increased risk of developing pulmonary hypertension.

All patients with DS who require anesthesia should have a preoperative evaluation to screen for the presence of multisystem disease. Patients should be examined for the presence of atlantoaxial instability with radiographic images such as MRI reserved for those with worsening muscle tone or increasing weakness. While the likelihood of a spinal injury under anesthesia in a child with DS is very low, efforts to limit extreme motions of the cervical spine are warranted in all patients with DS [11]. Patients with DS who require anesthesia should at some point have an ECG and echocardiogram to rule out the presence of congenital heart disease and pulmonary hypertension. Thyroid tests to detect hypothyroidism should be performed. Screening for snoring and obstructive sleep apnea should also be performed in all patients with DS who require anesthesia. Blood tests to evaluate for thrombocytopenia are warranted before procedures at high risk for blood loss.

Even with adequate preparation, patients with DS can be challenging for anesthesiologists. Difficult vascular access due to xeroderma and obesity is common. Patients may have

increased procedural anxiety which can be worsened by hearing difficulty and language delays. DS patients may have difficulty expressing pain, yet they may be more sensitive to the effects of opioids due to OSA. While it has long been rumored that patients with DS require higher doses of anesthesia, there is no evidence supporting this, and recent studies have all but disproven this hypothesis [22]. Anesthetic risk in patients with DS is dependent on the severity and presence of comorbidities with younger, lower-weight children with cardiac disease and pulmonary hypertension at the highest risk of complications. In a review of 930 non-cardiac anesthetics in patients with DS, the cohort of patients with trisomy 21 had an increased incidence of perioperative respiratory adverse events mostly due to an increased incidence of obstructed ventilation [23].

Trisomy 18 and 13

Trisomy 13 (Patau syndrome) and Trisomy 18 (Edwards syndrome), result from having three copies of chromosomes 13 and 18, respectively. Trisomy 18 is the second most common autosomal trisomy occurring in about 1/6,000 live births, while Trisomy 13 occurs in 1/10,000 live births [24, 25]. Antenatal diagnosis occurs in most cases due to maternal age, maternal serum markers (significantly lower human chorionic gonadotropin, unconjugated estriol, and alpha-fetoprotein), and sonographic changes of the nasal bone and nuchal translucency [23]. Later sonographic findings identify up to 90% of cases. While preterm loss, stillbirth, and elective termination occur in a large majority of cases, survival to term increases with increasing gestational age. Among those who survive to term, the risk of early death is very high, with recent studies showing a survival to 1 year in only 5–10% of children with both Trisomy 13 and 18 [24–26].

Multiple congenital anomalies are often present in children with Trisomy 13 and 18, and invasive procedures are likely needed for survival in most children with the syndrome. Low birthweight occurs in most children with each syndrome. Central nervous system abnormalities are likely to present leading to central apnea, severe developmental delay, and seizures. Feeding difficulties, gastroesophageal reflux, and growth retardation occur in most patients, and a permanent feeding tube is required in many patients. Respiratory insufficiency is multifactorial. Central apnea is common, and hypotonia, micrognathia, laryngotracheomalacia, and a high frequency of cleft lip and palate can lead to obstructive apnea. Because of this, many patients with Trisomy 18 and 13 require lifelong invasive ventilatory support.

Cardiac disease occurs in up to 80% of patients with Trisomy 18 and Trisomy 13, with ASD, VSD, patent ductus arteriosus (PDA), and valvular abnormalities being most common. Until recently, few centers chose to operate on patients with Trisomy 18. Today, most centers offer cardiac surgery for patients with Trisomy 18. A 2019 study of the Society of Thoracic Surgeons Congenital Heart Surgery Database of children with T13 and T18 who underwent cardiac surgery (2010–2017) demonstrated that while 70% of centers offered surgery on these patients, mortality remained high at 15% with a high rate of complications [27].



Figure 8.3 A 3 month old infant with trisomy 18 (Edwards syndrome). Note the microphthalmia, micrognathia, short neck, and failure to thrive. The infant was also hypotonic with club foot, and had ventricular and atrial septal defects. (Source: Bali et al. [25]. Reproduced with permission from Turkish Society of Anaesthesiology and Reanimation.)

Those who required preoperative mechanical ventilation had an 8-fold increased risk of mortality.

Preoperative evaluation of the airway, severity of cardiac disease, and consequences of prematurity is necessary for all children with Trisomy 18 and 13. Difficult intubation and ventilation should be anticipated in patients with Trisomy 18 and 13 because of micrognathia, high prevalence of cleft lip and palate, and a narrow palate [28] (Figure 8.3). Most patients with these chromosomal disorders will require prolonged postoperative mechanical ventilation due to prematurity, central apnea and airway obstruction.

Williams-Beuren syndrome and Elastin arteriopathies

Williams syndrome (WS) is caused by a deletion on the long arm of chromosome 7q11.22 which most notably codes for the protein elastin, important in the elasticity of blood vessels. Nonsyndromic elastin arteriopathies have similar cardiovascular presentations of WS without the extravascular abnormalities. Diagnosis of WS is typically by FISH (see below under Genetic Testing), demonstrating a segment loss on chromosome 7. Patients with WS are known for their characteristic elfin facies, with a broad forehead, wide mouth, a short-upturned nose, and epicanthal folds [29] (Figure 8.4). Many have a gregarious, friendly personality; however, periprocedural anxiety is common (14). Feeding difficulties and reflux are common and up to 50% of WS patients have hypercalcemia, especially in infancy. Up to 70% of patients with WS have cardiovascular diseases, most notably supravalvular aortic stenosis (SVAS), supravalvular pulmonary stenosis and ostial

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Figure 8.4 Williams syndrome facies in a young child. Note the periorbital puffiness, flat nasal bridge, long philtrum, wide smile, full cheeks, and full lower lip. (Source: Waxler et al. [48]. Reproduced with permission from SLACK Incorporated.)

stenosis of coronary arteries. Patients with severe outflow tract obstructions and/or coronary disease are at high risk for myocardial ischemia with induction of anesthesia [30, 31]. In addition to a 25% lifetime risk of sudden death in patients with WS, there were several cases of cardiac arrest under anesthesia documented in the literature with an estimated incidence of 5%. Several methods of risk stratification have been proposed in the literature, though prospective studies evaluating their accuracy have not been performed. All patients with WS who present for anesthesia should undergo risk stratification and perioperative planning, and it has been demonstrated that with such planning, the incidence of cardiac arrest may be minimized. Echocardiograms to evaluate the severity of supravalvar aortic and pulmonary stenosis, ECGs screening for latent ischemia should be performed on all patients with WS before anesthetic care. Evaluation of the coronaries should be performed in those with stenosis of the thoracic aorta, moderate to severe SVAS and those with signs of symptoms of ischemia. Both cardiac CT angiography and cardiac catheterization can be used to image the patency of the coronary arteries, with CT angiography having the advantage of being done without general anesthesia and avoiding the temporary interruption of coronary blood flow during catheter-based angiography which has been the cause of cardiac arrest in several patients with WS [32]. Younger patients (<3 years) with moderate to severe outflow tract gradients or those with biventricular outflow tract obstruction should be considered at high risk for myocardial ischemia during anesthesia (16). Such patients may benefit from preoperative hydration, the use of anesthesia drugs that maintain SVR and minimize myocardial oxygen consumption, and judicious use of vasopressors such as phenylephrine to maintain coronary perfusion pressure. All patients considered high risk should be cared for in centers with the capability for full resuscitation and the availability of extracorporeal membrane oxygenation (ECMO), as standard resuscitation measures may fail in patients with severe coronary stenosis or severe outflow tract obstruction. ECMO standby is used at several centers when caring for moderate to high-risk WS patients. Chapter 35 presents an extensive discussion of anesthetic risk stratification and approach in WS.

Noonan syndrome

Noonan syndrome (NS), occurring in 1/2,500 live births is the second most common genetic cause of congenital heart disease. Noonan syndrome typically occurs via autosomal dominant inheritance and is a heterogenous disease with a wide range of clinical characteristics. NS is considered a RASopathy, which results from germline mutations in the intracellular RAS/mitogen-activated protein kinase (MAPK) pathway [33, 34]. Diagnosis is suspected from fetal ultrasound and fetal echocardiography and can be confirmed by DNA sequencing. Distinctive facial features in patients with NS include a tall forehead, hypertelorism with prominent eyes and downslanting palpebral fissures, a small jaw and short, webbed neck, and low-set and posteriorly rotated ears and widespaced nipples with pectus excavatum [35] (Figure 8.5). Hearing and intellectual difficulties are common. Children with NS have short stature, feeding difficulties, and cryptorchidism in up to 80% of males (17, 18). Congenital heart disease occurs in over 80% of children with NS. Pulmonary valve stenosis is the most common congenital heart defect, occurring

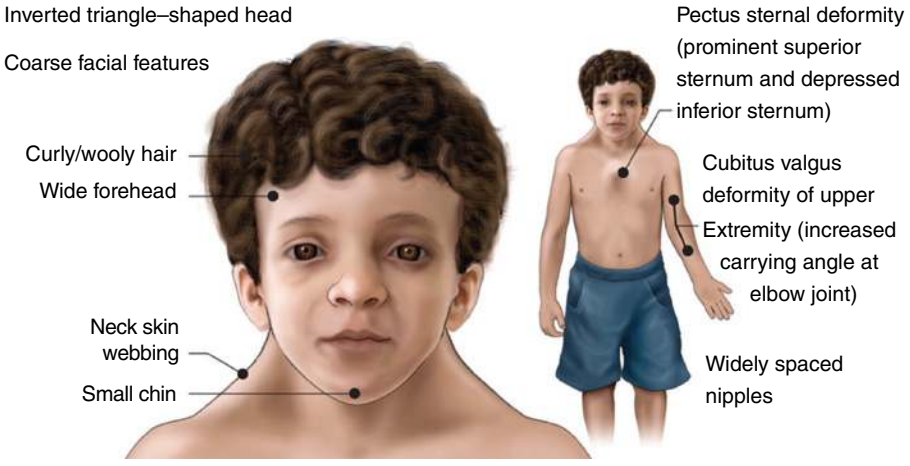


Figure 8.5 Noonan syndrome phenotypic features in a child. (Source: Bhambhani and Muenke [35] / American Academy of Family Physicians / Public Domain.)

in over 50% of patients. These dysplastic thickened pulmonary valve leaflets are often resistant to valvuloplasty. Atrial septal defect (ASD) is the second most common cardiac defect. Twenty percent of children with NS have hypertrophic cardiomyopathy often presenting as early as 6 months of age, far earlier than other forms of hypertrophic obstructive cardiomyopathy (HOCM) [33, 34, 36]. Among those NS patients with HOCM, obstruction of the left ventricular outflow tract and congestive heart failure are more common than typical HOCM patients. Earlier diagnosis and the presence of congestive heart failure symptoms are associated with worse long-term survival in patients with NS-associated HOCM [36].

Patients with NS who require anesthesia should have recent echocardiograms to screen for cardiac defects and to assess the severity of outflow tract obstruction. Patients with HOCM with moderate to severe left ventricular outflow tract (LVOT) obstruction should have preoperative IV placed for prehydration. Careful titration of induction agents with preservation of systematic vascular resistance while avoiding hypovolemia and tachycardia should be performed to minimize myocardial ischemia during anesthesia. Older patients with NS can have limited mouth opening and more severe micrognathia than infants due to joint immobility with advancing age, and difficult laryngoscopy should be anticipated.

Turner syndrome

Turner syndrome (TS), an X-linked chromosomal syndrome occurs due to loss of one sex chromosome (45XO). Prenatal diagnosis is often from chorionic villous sampling or amniocentesis. Affected females typically have short stature, a webbed neck, a broad chest with wide-spaced nipples, and gonadal dysgenesis [37, 38] (Figure 8.6). Airway anomalies include micrognathia, a narrow maxilla, and a high arched palate [39]. Swelling of the hands and feet due to lymphedema can occur and scoliosis is prevalent in up to 10% of children with Turner syndrome. Renal defects such as horseshoe kidney and renal agenesis can occur, and autoimmune diseases such as hypothyroidism and celiac disease occur with high prevalence [37].



Figure 8.6 A 14-year-old female with Turner syndrome. (Source: Acarturk [38]. Reproduced with permission from Springer Nature.)

The most common congenital heart defects in TS include a bicuspid aortic valve and coarctation of the aorta (CoA). Hypertension is common even in patients without CoA. These patients are at risk of aortic dissection and require lifelong evaluation of blood pressure and aortic dimensions [37].

A careful preoperative workup evaluating the presence and severity of cardiac disease, renal and thyroid function, and the airway is necessary before anesthetic care in patients with Turner syndrome. Difficult laryngoscopy and intubation should be anticipated due to limited neck mobility and retrognathia. Blood pressure lability as well as difficult vascular access may be encountered during anesthetic care [39].

Goldenhar syndrome

Interruption of the blood supply to the first and second brachial arches during the first trimester leads to oculo-auriculovertebral syndrome, also known as Goldenhar syndrome. Diagnosis typically occurs after birth after noting unilateral facial hypoplasia. Facial asymmetry, mandibular hypoplasia, eye abnormalities, microtia or absent ear on the affected side, and dental abnormalities of varying degrees are typically present [40]. Vertebral abnormalities including cervical vertebral fusion and vertebral hypoplasia are present in up to 60% of patients [40, 41] (Figure 8.7). Various degrees of hearing loss and intellectual disability can occur. Congenital heart defects, commonly ventricular septal defects as well as conotruncal defects have been noted in anywhere from 5 to 58% of patients with Goldenhar syndrome, but the actual prevalence of CHD in Goldenhar syndrome is likely closer to 20% [42].

Anesthetic concerns typically focus on airway management, noting that these patients are among some of the most difficult patients to intubate due to severe micrognathia, a hypoplastic, arched palate, airway deviation towards the affected side, limited neck mobility, and mouth opening. Preparation for difficult mask ventilation and laryngoscopy is mandatory when anesthetizing all patients with Goldenhar syndrome. While various techniques such as intubation through a laryngeal mask airway and video laryngoscopy have been employed successfully, preservation of spontaneous ventilation and having a plan should intubation attempts fail is necessary to avoid harm [43]. These patients often undergo several airway reconstructive surgeries to advance the mandible, though the success of these procedures in patients with Goldenhar syndrome is reported to be less than with other syndromes [44].

Mucopolysaccharidoses and glycogen storage diseases

Mucopolysaccharidoses (MPSs) are a collection of lysosomal storage diseases, caused by the functional deficiency of lysosomal enzymes from a genetic mutation in the pathways of the breakdown of glycosaminoglycans (GAG), which were previously termed mucopolysaccharides. These are rare metabolic disorders characterized by the accumulation of incompletely

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Figure 8.7 Goldenhar syndrome in a 7-year-old male. Note the facial asymmetry with hypoplastic mandible and ear deformity on the left side. (Source: Vendramini-Pittoli and Kokitsu-Nakata [42]. Reproduced with permission from Wolters Kluwer.)

degraded GAGs in virtually all tissues of the body. Classic phenotypes result, including dwarfism, bone and joint deformities, dysmorphic facial characteristics, developmental delay in some patients, ocular and hearing abnormalities, hepatosplenomegaly, and inguinal or umbilical hernias. Cardiac findings are frequent, but much more common in MPS I (Hurler, Hurler-Scheie Syndrome), MPS II (Hunter Syndrome), and MPS VI (Maroteaux-Lamy Syndrome) [45]. Table 8.1 presents the genetic inheritance, involved chromosomes, frequency, and cardiac and non-cardiac manifestations of these diseases [46–48]. In addition to the six major categories, each has several subtypes with a variable clinical phenotype that depends on the precise enzyme defect; thus presentation, including cardiac disease, is variable. The overall prevalence of these rare diseases together is 1 : 20,000 live births.

Cardiac valvular pathology is the most common manifestation, and leaflet thickening with dysfunction has been reported in more than 80% of patients with MPS I, 50–60% of patients with MPS II, and in essentially all patients with MPS VI [45]. Valvular regurgitation, not stenosis, is more common, and the mitral valve is most commonly affected rather than the aortic. Right-sided valvular disease is less severe. Markedly thickened mitral valve leaflets, and shortened cordae tendinae result in dysmorphic and poorly mobile leaflets. Coronary artery narrowing and occlusion by GAG deposition in proximal coronary arteries is most common in MPS I and II and can occur early, especially in rapidly progressing forms of the disease. Conduction abnormalities, consisting of bundle branch block or complete heart block are seen up to 40% of these patients, presumably from infiltration of the conduction system with GAGs. Valve repair or replacement is the most common cardiac surgery in patients with mucopolysaccharidoses.

In addition to the cardiac pathology, difficult intubation is the most common anesthetic challenge, and MPS I, II, and, VI have in common mucopolysaccharide deposits in the lips, tongue, epiglottis, tonsils, adenoids, and lower airway making them at high risk for airway obstruction and difficult laryngoscopy. In addition, many have a short, stiff neck, and cervical spine abnormalities including atlantoaxial instability and foraminal stenosis[49] (Figure 8.8). A complete preanesthetic evaluation including these and other involved organ systems and a plan to manage them is crucially important for these diseases [46]. Of particular concern if regional anesthesia is contemplated are case reports of paralysis after combined general/epidural anesthesia in Hurler and Morquio Syndromes (MPS IV); avoiding neuraxial anesthesia is recommended in these patients [50].

Pompe Disease is a glycogen storage disease, which is a group of diseases that share defects in the enzymes that break down glycogen. Pompe Disease has an infantile, juvenile, and adult form, depending on the degree of alpha-glucosidase deficiency [51]. Glycogen deposits within the cardiac myocytes result in hypertrophic cardiomyopathy, which varies with the enzyme deficiency and can be severe, resulting in biventricular outflow tract obstruction. Alternately, some patients demonstrate dilated cardiomyopathy. Danon Disease is an even more rare X-linked disorder that can also result in hypertrophic or dilated cardiomyopathy. Imaging studies, non-cardiac surgery, and cardiac surgery for resection of hypertrophied myocardium to relieve outflow tract obstruction are common anesthetics in this population.

Enzyme replacement therapy (ERT) has been available for the last decade or more for MPS I, II, IV, VI, and VII; which consists of weekly intravenous infusions of the defective enzyme, produced using recombinant DNA

Table 8.1 Cardiac genetic syndromes

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
Alagille syndrome		Intracranial hemorrage/stroke; Developmental delay	90% with cardiovascular anomalies; most commonly branch pulmonary artery stenosis		Spontaneous bleeding of unknown etiology	Airway: unusual facies, possible cervical spine abnormalities with no reports of difficult intubation
Alagille-Watson syndrome, cholestasis with peripheral pulmonary stenosis, arteriohepatic dysplasia, syndromatic hepatic ductular hypoplasia			Other cardiac lesions: tetralogy of Fallot, tricuspid atesia, patent ductus arteriosus, ventricular septal defect		Biliary excretion abnormalities more than synthetic/metabolic hepatic abnormalities,	Abdominal distension may predispose to gastroesophageal reflux
Autosomal dominant					Butterfly Vertebrae; Possible shortened interpedicular distance,	Neurologic assessment, avoid succinylcholine with myopathies
1 : 70,000					exocrine pancreatic insufficiency	Cardiac work-up
Chromosome 20p12 microdeletion					Renal disease	Assess coagulation profile – caution with neuraxial analgesia/anesthesia
JAG 1 signaling gene, encodes a ligand for the NOTCH1 receptor, critical for the determination of cell fates in early development					Vitamin K malabsorption – coagulopathies	Caution with positioning – rickets/hepatic osteodystrophy
					Vitamin D malabsorption – rickets/pathologic fractures	
					Vitamin E malabsorption – peripheral myopathy/neuropathy	
					Liver transplant frequent in severe Alagille's	
CHARGE association	Swallowing/sucking difficulties	Colobomata: typical iris coloboma to anophthalmos	Right-sided congenital heart disease: tetralogy of Fallot, pulmonic stenosis, double outlet right ventricle	Atresia Choanae	Hypogenitalism	Possible difficult/impossible endotracheal intubation with micrognathia
Parental gonadal mosaicism in some cases; spontaneous mutation	Cleft palate associated with congenital heart disease, mostly tetralogy of Fallot	Cranial nerve dysfunction: CNI – anosmia, CN-VII – facial palsy, CN-VIII – hearing loss, CN-IX/CN-X – velopharyngeal incordination	atrioventricular septal congenital heart disease: ventricular/ atrial septal defect associated with tetralogy of Fallot	tracheoesophageal fistula associated with congenital heart disease, mostly tetralogy of Fallot	Renal anomalies (malrotation, hydronephrosis, reflux) associated with congenital heart disease, mostly atrioventricular septal defect	May require continuous positive airway pressure to maintain airway patency with laryngomalacia/velopalatal insufficiency
1 : 10,000	Hypoplastic mandible (micrognathia) associated with congenital heart disease, mostly tetralogy of Fallot	Delayed motor development, may involve truncal hypotonia	Aberrant subclavian artery and/or right aortic arch		Vertebral anomalies (hemivertebrae, scoliosis) associated with congenital heart disease	May require smaller than expected endotracheal tube for subglottic stenosis

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Heterozygous mutation in the CHD7 on chromosome 8q12.	Semicircular canal agenesis, sensorineural or conductive hearing loss	Developmental delay			
Chromodomain helicase DNA binding protein 7 (CHD7) gene–neural crest epigenetic chromatin remodeling	Three major issues: micrognathia, laryngomalacia, subglottic stenosis				Aspiration risk with swallowing dysfunction, cardiac work-up for congenital heart defects, Thyroid/Parathyroid functional studies for similarities between CHARGE and DiGeorge syndromes High incidence of post-operative airway events Successful airway management with laryngeal mask airway has been reported
DiGeorge (22q11-) syndrome	Craniofacial anomalies: Cleft palate, micrognathia, small mouth	Learning difficulties, other pyschiatric disorders	Cardiac defects: tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, pulmonic stenosis, tricuspid atresia	Hypo- or aplasia of parathyroid gland resulting in hypocalcemia	Reports of vasomotor instability
(Velocardiofacial Syndrome, CATCH-22, conotruncal anomalies face syndrome)	Small thyroid cartiledge with increased anterior angle			Hypo- or aplasia of thymus gland resulting in immune deficiencies	Cardiac work-up for congenital heart disease
sporadic or autosomal dominant					
One in two thousand	Short trachea with a reduced number of cartilage rings			Renal & Skeletal anomalies	Possible difficult airway with dysmorphic faces
1.5- to 3.0-Mb hemizygous deletion of chromosome 22q11.2	Laryngobronchialmalacia			DiGeorge anomaly is likely a feature of Velocardiofacial Syndrome	Possible difficult extubation with velopharyngeal insufficiency
TXB1 deletion causes most cardiac defects and other phenotypic features; T-box genes are transcription factors involved in the regulation of developmental processes	Tracheal bronchi				Recurrent infection risk with thymic dysfunction, Persistent hypocalcemia with parathyroid dysfunction leading to seizures, report of tachycardia from epinephrine injected with local anesthetics

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
Down syndrome	High arched narrow palate, macroglossia, subglottic stenosis	Variable intellectual disablity	50% with congenital heart disease: Endocardial cushion defects (50%), ventricular septal defect, patent ductus arteriosus,tetralogy of Fallot	Upper airway obstruction/sleep apnea	Dental abnormalities	Radiologic cervical spine abnormalities do not correlate to neurologic symptoms
Trisomy 21	Obstructive sleep apnea				Higher risk for leukemia	
Errors in meiosis that lead to trisomy 21 are overwhelmingly of maternal origin; only about 5% occur during spermatogenesis.	Atlanto-axial subluxation	Possible altered response to opioids	Predisposed to pulmonary hypertension		Duodenal atresia, Hirschsprung's disease with gastroesophageal reflux	Atlantoaxial instabilitity may increase with loss of muscle tone under anesthesia
1 in 650–1,000	Smaller tracheal lumen diameter	Hypotonia	Predisposed to bradycardia with inhaled induction; halothane, sevoflurane		Immunosuppression and hypothyroidism	Smaller enotracheal tube (0.5–1 mm)) to avert tracheal trauma
Transient myeloproliferative disorder and megakaryoblastic leukemia of Down syndrome are associated with mutations in the GATA1 gene. Somatic mutations in the JAK2 gene are associated with acute lymphoblastic leukemia			Possible difficult arterial/venous access		Hypotonia, hyperextensibility, dysplastic pelvis	Possible difficult vascular access, Possible bradycardic response to high concentration volatile anesthetic agents
Ehler-Danlos Syndrome (EDS)	Dysphonia - hemi-laryngeal weakness	Mild/mod weakness, myalgia, and easy fatigability in the majority of patients	Bleeding symptoms for all EDS types			Bleeding symptoms are responsive to desmopressin
EDS – Classical type			Mitral valve prolapse, aortic root/sinus of Valsalva dilatation, septal defects		Classic: I and II – Skin hyperextensibility, widened atrophic scars, joint hypermobility	Report of scoliosis correction using spinal fusion complicated by bleeding and wound dehiscence (D-29.11)
autosomal dominant disorder type V collagen; chromosome 9q34.3; 1 : 20–50,000						
EDS – Hypermobility type		Decreased/absent analgesic effect from lidocaine given subcutaneously, or local anesthetic cream	Mitral valve prolapse, aortic root/sinus of Valsalva dilatation, septal defects		Hypermobility: III – Hyperextensibility ± smooth, velvety skin, generalized joint hypermobility	
autosmal dominant or recessive mutation in tenascin X gene						
EDS – Vascular type			Medium and large-size vessel fragility leading to rupture		Vascular: IV – Translucent skin, arterial/intestinal/ uterine fragility, extensive brusing, characteristic faces	Premature death from organ rupture (arterial, bowel, uterus)

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Autosmal dominant mutation in type III collagen gene: 1 : 100–250,000						Report of success using Recombinant Factor VIIa
EDS – Kyphoscoliosis type	Atlantoaxial subluxation may occur in Type IV				Kyphoscoliosis: VI – Joint laxity, muscle hypotonia, progressive scoliosis, scleral fragility	Report of scoliosis correction using spinal fusion complicated by arterial avulsion/rupture
autosomal recessive mutation in gene for lysyl hydroxylase: fewer than 60 cases						
EDS – Arthrochalasia type					Arthrochalasia: VIIA/B – Joint laxity with recurrent subluxations, congenital B/L hip dislocation	
Mutation in type I collagen gene; fewer than 30 cases						Careful positioning and skin protection
EDS – Dermatosparaxis type					Dermatosparaxis: VIIC – Severe skin fragility, sagging, redundant skin	Gentle intubation with minimal inspiratory pressures to avoid airway hematomas
10 cases reported						Consider possible cervical instability
13 subtypes recognized in 2017 reclassification						Cardiac work-up to assess valves and great vessels Avoid central vascular access or place under U/S visualization Prepare for significant blood loss Caution with neuraxial anesthesia/analgesia
Pompe disease: glycogen storage disease type II	Infantile onset: macroglossia	Infantile onset: rapidly progressive muscle weakness – axial hypotonia, areflexia	Infantile onset: cardiomegaly/ cardiomyopathy leading to cardiac failure	Infantile onset: respiratory insufficiency with frequent infections	Infantile onset: hepatomegly, elevated creatine kinase	Respiratory insufficiency & hypertrophic cardiomyopathy pose a significant anesthetic risk
Acid maltase deficiency						Maintain intravascular volume and diastolic blood pressure for coronary perfusion
1 : 60–140,000						Reports of arrhythmias due to decreased coronary perfusion with propofol Reports of successful regional anesthetic techniques
	Late-onset: macroglossia is infrequent	Late onset: progressive proximal muscle weakness – lower > upper extremity, Gower sign, decreased deep tendon reflexes	Late-onset: cardiomegaly/ cardiomyopathy is uncommon	Late onset: respiratory insufficiency/failure with infections, dyspnea on exertion,obstructive sleep apnea, Orthopnea	Late onset: moderate hepatomegaly, scoliosis/ kyphosis/lordosis	Respiratory insufficiency poses anesthetic risk

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
						Hypotonia/wheelchair-bound – avoid neuromuscular blocking drugs and succinylcholine for prolonged weakness and hyperkalemia Reports of prolonged respiratory depression with volatile agents
Goldenhar syndrome	Unilateral facial hypoplasia: prominent forehead, zygomatic hypoplasia, maxillar/mandibular hypoplasia	Epibulbar dermoid/ ipodermoid, eye anomalies; microphthalmia, anophthalmia, etc	30–60% CHD: 40% conotruncal, 30% septal, 15% targeted growth, 7% situs/looping, 4% left-sided obstruction		Vertebral anomalies: hemivertebrae, fused vertebrae, scoliosis	Difficult airway – reports of failed intubation
Hemifacial microsomia, oculo-auriculo-vertebral syndrome, facio-auriculo-vertebral syndrome	Unilateral macrostomia – lateral facial cleft	Preauricular skin tag/blind fistulas, microtia or other external ear malformations			Often with rib/extremity anomalies	Reports of successful intubation with multiple techniques
Most cases are sporadic mutations; autosomal recessive or autosomal dominant reported	Vertebral anomalies: atlas occipitalization, synostosis	Vertebral anomalies; bifid spine			genitourinary anomalies: ectopic kidney, renal agenesis, vesicuolureteral reflux, ureteropelvic junction obstruction	Evaluate cervical spine for instability
1 in 5,600	Laryngotracheal anomalies: Cartilaginous tracheal sleeve	Often with occipital encephalocoele				Cardiac work-up
Mutation in hemifacial microsomia gene on chromosome 14p32 in some patients	Significant incidence of C1–C2 instability	Often with complex retardation of development				
	Often with Cleft lip/palate/tongue, unilateral tongue hypoplasia, parotid gland aplasia					
	Often with tracheoesophageal fistula/esophageal atresia					
Heterotaxy syndrome	Infrequent: cleft lip/palate, micrognathia, choanal atresia, laryngeal cleft	Rare: Neural tube defects, encephalocoele, cerebellar or corpus callosum agenesis	High prevalence of CHD	Abnormal ciliary function in up to 40%; frequent respiratory infections	Intestinal malrotation; polysplenia, asplenia, transverse liver,	
X-linked; chromosome Xq26.3; Autosomal dominant: heterozygous mutation in CFC1 gene on chromosome 2q21.			Single ventricle; DORV, TAPVR, right or left atrial isomerism,dual or absent SA nodes, bilateral SVC, interrupted IVC, unbalanced AVSD,	Bilateral right or left lungs and bronchi	Rare: hemivertebra, sacral agenesis, hypoplastic kidneys, hypospadias	

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Multiple additional genes in phenotypic series: on chromosomes 3p22.2, 6q21, 7p12.3,10q22.1, 10q26.2,15q21.3,18q21.1			Cardiac arrhythmias: bradycardia in left atrial isomerism, atrial tachycardias in right atrial isomerism		
1 : 5,000–10,000 live births					
Hunter syndrome	Dural hyperplasia/thickening ligamentum flavum lead to cervical myelopathy with UMN signs	Normal intelligence with progressive neurodegeneration leading to vegetative state as teenagers	Cardiac disease: cardiomyopathy, asymmetric ventricle septal thicking, mitral/aortic valve thickening	GI dysfunction: idiopathic diarrhea, spontaneous gastric perforation, bowel pseduo-obstruction	Difficult airway: short neck, high larynx, large tongue, cervical instability
Mucopolysaccharidosis Type II	Coarse facies	Narrowing of the bony neural canal predisposing to cervical cord compression	Sudden death - likely arrhythmia from coronary insufficiency	Treatment with enzyme replacement therapy or stem cell transplantation with limited success	Reports of post-obstructive pulmonary edema at induction/extubation,
X-linked recessive	temperomandibular joint stiffness and short, stiff neck	Compressive myelopathy from meningeal thickening causing communicating hydrocephalus			Reports of successful intubation using multiple techniques: blind nasal, fiber optic, LMA
1 : 110–320,000 males	Adenotonsillar hypertrophy contributing to obstructive sleep apnea, progressive upper airway obstruction, infections				Reports of intubation failure using laryngeal mask airway
Mutation in the gene encoding iduronate 2-sulfatase (IDS) on chromosome Xq28	Glycosaminoglycan deposition in pharynx/larynx wall – laryngeal inlet prolapse/stridor/airway compromise				Report of delayed awakening following a single dose of opioid
Deficient enzyme, iduronate-2-sulfatase: is involved in the lysosomal degradation of the glycosaminoglycans heparan sulfate and dermatan sulfate	Progressive tracheal deformation; cricoid to lower bronchi				
	Trauma (airway instrumentation) may induce mucopolysaccharide deposition				
	C1 and C2 subluxation with odontoid dysplasia				
Hurler syndrome	Facial dysmorphism, obstructive sleep apnea is nearly universal	Developmental disability	Cardiac disease: cardiomyopathy, asymmetric ventricle septal thicking, mitral/aortic valve thickening	Progressive joint stiffness with decreased mobility, severe back pain, lumbar spondylolisthesis with cord compression	Difficult airway: short neck, high larynx, large tongue, cervical instability
Mucopolysaccharidosis type I	Coarse facies/gum hypertrophy, macroglossia	Possible hydrocephalus	Sudden death – likely arrhythmia from coronary insufficiency	Poor hand function likely from carpal tunnel syndrome	Epiglottis tip behind soft palate – oral airway exacerbates not relieves the obstruction
Autosomal recessive	TMJ stiffness and short stiff neck		mitral/aortic valve dysplasia, left ventricular hypertrophy, normal function – same or better following bone marrow transplant	Hepatosplenomegaly – likely leading to a high incidence of umbilical hernia	Reports of postobstructive pulmonary edema at induction/extubation

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
1 : 100,000	Adenotonsillar hypertrophy contributing to obstructive sleep apnea, progressive upper airway obstruction, infections				Treatment with enzyme replacement therapy, stem cell, or cord blood transplantation has had some good long term results	Reports of successful intubation using multiple techniques
homozygous or compound heterozygous mutation in the gene encoding alpha-L-iduronidase (IDUA) on chromosome 4p16.3	Glycosaminoglycan deposition in pharynx/larynx wall – laryngeal inlet prolapse/stridor/airway compromise					Report of failed epidural anesthesia – likely from mucopolysaccharide deposits on meninges
Iduronidase deficiency: hydrolyzes the terminal alpha-L-iduronic acid residues of the glycosaminoglycans dermatan sulfate and heparan sulfate	Ocular findings: corneal clouding, glaucoma					
Hurler-Scheie, and Scheie are milder forms of disease						
Loeys-Dietz syndrome	Widely spaced eyes, bifid uvula/cleft palate	Cerebral aneurysms	Aortic, thoracic, and abdominal arterial aneurysms and/or dissections	Pectus excavatum or carinatum	Unstable vertebral subluxations. Arachnodactyly, camptodactyly, clubfoot deformity, scoliosis, joint laxity.	Similar to Marfan Syndrome but earlier/worse aortic aneurysms.
Furlong syndrome		Craniosynostosis				Possible micrognathia
Autosomal dominant		Normal intelligence				Possible cervical spine abnormalities
Transforming growth factor-beta receptor 1 and 2 genes: 4 of the 5 types						Beta blocker and ACE receptor blocker/inhibitor therapy common
						Control hypertension/tachycardia
Marfan syndrome	High-arched palate	The widened lumbosacral canal may lead to increased cerebrospinal fluid volume: may need larger than normal doses of spinal or epidural anesthetics	Aortic dissection: avoid hypertension	Pectus excavatum	Characteristic facies:	Widened lumbosacral canal may lead to increased cerebrospinal fluid volume: may need larger than normal doses of spinal or epidural anesthetics
	Crowded teeth	Spinal arachnoid cysts	Mitral valve prolapse	Pulmonary blebs with spontaneous pneumothoraces	Dolichocephaly, long and narrow facies	avoid hypertension

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Variable inheritance; often autosomal dominant			Aortic or pulmonary artery dilatation: consider pre-operative echocardiography to confirm the absence	Obstructive sleep apnea	Lens dislocation, elongated globe, myopia	
1 : 3–10,000			Aortic insufficiency	Possible tracheomalacia	Increased risk of glaucoma, retinal detachment	
Heterozygous mutation in the fibrillin-1 gene (FBN1; 134797) on chromosome 15q21.1			Possible progressive narrowing of coronary arteries	Possible emphysema and bronchogenic cysts	Orthopedic abnormalities:	
Mutation fibrillin-1 gene: connective tissue protein					Tall with arm span greater than height Winged scapula Joint laxity leading to recurrent dislocations Ulnar deviation, arachnodactyly Scoliosis, kyphosis Congenital contractures, flat feet Gastrointestinal/genitourinary abnormalities: Inguinal, umbilical, and femoral hernias	
Maroteaux-Lamy syndrome	Possible difficult to impossible direct laryngoscopy and intubation:	Normal intelligence	Heart failure is the most common cause of death	At risk for airway obstruction: possible post-operative respiratory distress, post-obstructive pulmonary edema	Characteristic facies:	Cervical spinal cord compression
Mucopolysaccharidosis VI	Frontal bossing	Spinal compression from dural thickening, usually cervical: avoid neck extension	Aortic valve calcifications	Pectus carinatum	Coarse face, "tight" skin	Possible difficult intubation
Arylsulfatase B deficiency	Depressed nasal bridge	Communicating hydrocephalus from lumbar stenosis	Possible mitral valve involvement	Recurrent upper respiratory infections	Hirsutism	
Autosomal recessive	Enlarged tongue, gingival hypertrophy	Hearing loss: conductive and sensorineural	Hypertension	Sleep apnea	Corneal clouding	
1 : 238–433,000	Thick mucous secretions	Atlanto-axial instability from odontoid dysplasia		Restrictive lung disease	Orthopedic abnormalities:	
Homozygous or compound heterozygous mutation in the ARSB gene on chromosome 5q14.1	Short, stiff neck				Normal growth for the first few years, then stops	

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
Deficient arylsulfatase B; the lysosomal enzyme that removes the C4 sulfate ester group from the ***N***-acetylgalactosamine sugar residue at the nonreducing terminus of the glycosaminoglycans dermatan sulfate and chondroitin sulfate	Anterior larynx				Hypoplasia of hip acetabulae with small flared iliac wings	
	Possible atlanto-axial instability Intubation difficulty worsens with age At risk for airway obstruction due to mucopolysaccharide deposits in the lips, tongue, epiglottis, tonsils, adenoids, lower airway Loss of tonicity in the supraglottic region due to neuromuscular blockade might cause airway obstruction during manual ventilation; as such, consider not using neuromuscular blocking agents until the airway is secured.				Hypoplasia of L1–L2 vertebrae with lumbar kyphosis Proximal femoral dysplasia Contractures of joints due to deposits of polysaccharide in ligaments Restricted mobility of hips, knees, elbows Carpal tunnel syndrome, claw hand Hepatosplenomegaly with hypersplenism: Results in anemia, thrombocytopenia, genitourinary abnormalities: umbilical and inguinal hernias	
Morquio syndrome	Possible difficult mask ventilation, direct laryngoscopy, and intubation:	Cervical spine instability, odontoid hypoplasia with atlantoaxial subluxation: evaluate cervical spine pre-operatively	Mitral and aortic valve disease, especially aortic insufficiency late in the disease	Restrictive lung disease from kyphoscoliosis	Type A: severe form	Difficult airway tools that displace a significant amount of soft tissue in a rigid manner are preferable such as a video laryngoscope
Mucopolysaccharidosis IV	Short neck with limited movement	Sensorineural or mixed hearing loss	Possible pulmonary hypertension, cor pulmonale due to lung disease	Pectus carinatum, rib flaring	Type B: milder form	

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Mucopolysaccharidosis IVA	Neck flexion may occlude the airway	Normal intelligence		Obstructive or central sleep apnea	Characteristic facies:	
Galactosamine-6-sulfatase deficiency	Cervical spine instability			Recurrent lower airway infections	Dense calvarium	
Autosomal recessive	Possible limited mouth opening			Susceptible to pulmonary hemorrhage after bone marrow transplant	Coarse facial features	
1 : 216–640,000 (A and B)	Prominent mandible or maxilla				Short, antevered nose	
Mutation chromosome 16q24.3	Redundant pharyngeal mucosa				Short neck with limited movement	
Deficiency in galactosamin-6-sulfatase; lysosomal enzyme involved in the catabolism of keratan and chondroitin sulfate	Macroglossia				Broad mouth with redundant pharyngeal mucosa	
	Tonsillar and adenoid hypertrophy				Macroglossia	
Mucopolysaccharidosis IVB	Widely spaced maxillary anterior teeth				Widely spaced maxillary anterior teeth	
Autosomal recessive	May require smaller than predicted endotracheal tube				Corneal clouding, glaucoma	
1 : 216–640,000 (A and B)	Enamel hypoplasia with pitting (type A)				Orthopedic abnormalities:	
Mutation chromosome 3p22.3	Possible copious tracheobronchial secretions: consider antisialogogue				Short stature due to shortened trunk and neck	
Deficiency in beta-galactosidase; lysosomal hydrolase that cleaves the terminal beta-galactose from ganglioside substrates and other glycoconjugates					Shortened long bones, short hands, Odontoid hypoplasia with atlanto-axial subluxation, Flattened vertebral bodies (platyspondyly) Kyphoscoliosis, lumbar lordosis Joint laxity and instability: needs careful intraoperative positioning, Genu valgum GI abnormality: hepatosplenomegaly	
Noonan syndrome	Possible difficult intubation:	Arnold-Chiari malformation	Pulmonic stenosis	Pectus excavatum	Characteristic facies:	May be difficult to place epidural due to relatively narrow spinal canal with normal-sized spinal cord

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
Male Turner syndrome; Female Pseudo-Turner Syndrome; Turner Phenotype with Normal Karyotype	Webbed, short neck	Cerebral arteriovenous malformation	Hypertrophic obstructive cardiomyopathy	Kyphoscoliosis, thoracic lordosis	Triangular face	Possible difficult peripheral intravenous access due to subcutaneous edema
Autosomal dominant	Micrognathia		Bleeding diathesis – coagulation factor deficiency, platelet dysfunction, thrombocytopenia	Restrictive lung disease	High- arched eyebrows,	
1 : 1,000–2,500	Dental malocclusion	Possible hearing loss	Left ventricle hypertrophy		Downward slanting palpebral fissures	
Heterozygous mutation in the PTPN11 gene on chromosome 12q24.13(about 50% of patients; wide genotypic and phenotypic variability	Flat midface with depressed nasal bridge	Mild mental retardation	Patent ductus arteriosus		Epicanthal folds	
PTPN11 gene: protein tyrosine phosphatase SHP-2: modulates intercellular signaling including epidermal growth factor receptor	High arched palate		Aortic stenosis		Ptosis	
	Possible cervical cystic hygroma		Coarctation of the aorta		Myopia Strabismus Nystagmus Low set ears with thickened helix Orthopedic abnormality: short stature gastrointestinal abnormalities: Hepatosplenomegaly Poor feeding in infancy genitourinary abnormalities: Renal dysfunction, cryptorchidism genitourinary abnormalities: Lymphatic dysplasia	
Trisomy 13	Possible difficult direct laryngoscopy and intubation:	Hypotonia	Congenital heart defects:	Possible apnea: monitor post-operatively	Characteristic facies:	Spinal dysraphism: confirm absence prior to neuraxial technique

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Patau syndrome	Microcephaly: may require smaller than predicted endotracheal tube size	Myelomeningocele	Ventricular septal defect, Tetralogy of Fallot	Pectus carinatum	Microcephaly with occipital scalp defect
Sporadic: meotic non-dysjunction	Wide sagittal suture and fontanelles		Double-outlet right ventricle	Kyphoscoliosis	Low-set ears, abnormal helices
1 : 10,000	May require smaller than predicted endotracheal tube size	Developmental delay			Broad, flat nose
Chromosome 13 trisomy	Cleft lip or cleft palate	Febrile seizures			Microphthalmia, anophthalmia, cataracts
	Short neck	Holoprosencephaly with agenesis of the corpus callosum			Optic nerve hypoplasia, limited vision
	Micrognathia	Cerebellar hypoplasia			Short neck Capillary hemangioma on forehead, GI abnormalities: Microscopic pancreatic dysplasia Malrotation, omphalocele, Meckel's diverticulum, GU abnormalities: Unilateral renal agenesis, renal and urogenital duplication Hydronephrosis, polycystic kidneys Renal insufficiency Cryptorchidism, hypospadias Hypoplastic ovaries, abnormal insertion of fallopian tubes Orthopedic abnormalities: Polydactyly of hands, possibly feet Flexion deformities of hands, simian crease Radial aplasia Prominent heel, rocker-bottom foot deformity, clubfoot deformity Joint subluxation
Trisomy 18	Possible difficult direct laryngoscopy and intubation:	Sensorineural hearing loss	Greater than 95% incidence of cardiac defects:	Short sternum	Characteristic facies:

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
Edwards syndrome	Microcephaly, prominent occiput, narrow bifrontal diameter	Severe mental retardation	Ventricular septal defect, atrial septal defect, patent ductus arteriosus, bicuspid aortic valve	Possible diaphragmatic muscle hypoplasia,	Microcephaly, prominent occiput	
Sporadic: meotic non-dysjunction	Micrognathia	Hypotonia in the neonatal period	Pulmonic stenosis, coarctation of the aorta	the absent or malformed right lung	Short palpebral fissures	
1 : 6–8,000	Cleft lip or cleft palate	Hypertonia after the neonatal period	Aberrant subclavian artery: confirm absence prior to placement of subclavian central venous line	Recurrent apnea in the neonatal period	Epicanthal folds, ptosis, corneal opacity	
Chromosome 18 trisomy		Possible holoprosencephaly			Low-set, malformed ears gastrointestinal abnormalities: Omphalocele, Meckel's diverticulum, malrotation Anal anomalies, ectopic pancreatic or splenic tissue Failure to thrive genitourinary abnormalities: Cryptorchidism Ectopic kidneys, horseshoe kidney, polycystic kidney Hydronephrosis, duplication of the collecting system Renal insufficiency Orthopedic abnormalities: Clenched hands at birth, index finger overlaps third finger, fifth finger overlaps the fourth Short, hypoplastic, or absent thumb Small, narrow pelvis with limited hip abduction Clubfoot deformity, rocker-bottom feet, syndactyly of second and third toes, short stature	

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Turner syndrome	Possible difficult intubation:	Sensorineural hearing loss	Congenital heart anomalies:	Broad, "shield-like" chest	Occurs in females
XO syndrome	Short, webbed neck: possible endobronchial intubation		Coarctation of the aorta	Mild pectus excavatum	Characteristic facies:
gonadal dysgenesis	High-arched palate		Bicuspid aortic valve		Webbed neck
meiotic nondisjunction, mosaicism	Micrognathia		Aortic dissection		Ptosis, inner canthal folds
1 : 2,500 females			Partial anomalous venous return		Protruding external ear
monosomy chromosome X			Possible prolonged QT		Strabismus, amblyopia
Half of the patients are mosaic (45 XO/46 XX) with milder manifestations			Hypertension		Orthopedic abnormalities:
			Hypercholesterolism		Short stature
					Increased carrying angle of elbows
					Short fourth metacarpal and metatarsal
					Narrow, deeply set nails
					Dislocated hips, puffy hands and feet
					Scoliosis, kyphosis
					Dislocation of patella
					gastrointestinal abnormalities:
					Crohn's disease, ulcerative colitis
					genitourinary abnormalities:
					Gonadal dysgenesis or agenesis with streak ovaries
					Fertility is rare
					Horseshoe kidney
					Possible duplicated collecting system
					Endocrine abnormalities:
					Absent thelarche and menarche: may be on hormone therapy
					Sometimes receive growth hormone replacement therapy
					Insulin resistance with type II diabetes
					Hypothyroidism

(*Continued*)

Table 8.1 (Continued)

Syndrome: Name, Eponyms, Inheritance,Incidence,Gene Locus, Gene Product	HEENT/Airway	Central nervous system	Cardiovascular	Pulmonary/Thoracic	Other	Additional anesthetic considerations
VACTERL/VATER Sporadic inheritance 1 : 17,000 Possible defects at chromosome 2,7,16 (animal models) Candidate genes: SHH, FOX gli	Laryngeal stenosis Tracheal atresia Possible choanal atresia: cannot place nasal airway, perform nasal intubation, or place nasogastric tube	Vertebral anomalies: hemivertebrae, dysplastic vertebrae, vertebral fusion, tethered cord	Cardiac malformations	Tracheoesophageal fistula Ectopic bronchus	Obesity GI abnormalities: Anal atresia Trachoesophageal fistula Esophageal atresia Duodenal atresia Orthopedic abnormalities: Radial dysplasia Vertebral anomalies: hemivertebrae, dysplastic vertebrae, vertebral fusion Dysplastic thumb Preaxial polydactyly, syndactyly Hip dysplasia GU abnormalities: Renal dysplasia Defects of external genitalia	
Williams syndrome	Possible difficult intubation:	Cerebral artery stenosis	Congenital heart defects:		Characteristic facies:	High incidence of coronary artery abnormalities and obstruction even if the supravalvar aortic stenosis is not severe. Avoid hypotension and hypovolemia, tachycardia. Avoid prolonged fasting and anesthetic drugs that excessively veno- and vasodilate. Have volume infusion, and bolus vasoconstrictor agents available (phenylephrine).

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Williams-Beuren syndrome	Flat mid-face, wide mouth	Infantile hypotonia with hypertonia later	Aortic stenosis, usually supravalvular,can lead to sudden death,	"Elfin" facies
Autosomal dominant or spontaneous inheritance	Dental malocclusion, poor dentition	Visuospacial deficits	Bicuspid aortic valve, mitral valve prolapse, mitral insufficiency	Puffy eyes, lacy iris pattern
1 : 10,000		Attention deficit disorder	Left coronary artery stenosis, myocardial ischemia	Hyperacusis
Deletion chromosome 7q11.23		Hyperacusis	Peripheral pulmonary artery stenosis	Depressed nasal bridge with anteverted nares
Gene: elastin		Seizures	Abdominal aortic coarctation	Enamel hypoplasia with small teeth
			Tetralogy of Fallot, ventricular septal defect	Harsh voice
			Possible narrowing of celiac, mesenteric, or renal arteries	Orthopedic abnormalities:
			Hypertension	Short stature
			Sudden cardiovascular collapse and death	Hypoplastic nails
				Hallux valgus, progressive joint limitation
				gastrointestinal abnormalities:
				Chronic constipation, diverticulosis genitourinary abnormalities:
				Renal structural anomalies
				Nephrocalcinosis, recurrent UTIs
				Renal artery stenosis
				Endocrine abnormalities:
				Neonatal hypercalcemia
				Early menarche
				Possible hypothyroidism
				Musical ability
				Friendly, "cocktail party" personalities

References for gene mapping, gene product, incidence, and inheritance: Reference 47: United States National Institutes of Health Mendelian Inheritance in Man; OMIM®: Online Mendelian Inheritance in Man; https://www.omim.org, accessed September 22, 2021; Reference 47: Orphanet: the portal for rare diseases and orphan drugs. https://www.orpha.net/consor/cgi-bin/index.php?lng=EN, accessed September 22, 2021.

Source: Modified from Mann et al. [46].



Figure 8.8 Twelve-year-old boy with Hurler Syndrome and corneal opacity who presented for ophthalmologic surgery, with typical phenotype. (A) Short stature. (B) Coarse facial features with mucopolysaccharide deposits in the lips, tongue, epiglottis, tonsils, adenoids. (C) Short neck with low set ears. (D) Short fingers with joint stiffness. (E) Enlarged liver and spleen with an umbilical hernia. (F) Hallux valgus. The authors commented that the case was performed with a laryngeal mask airway, "as intubation was not possible." (Source: Sati et al. [49]. Reproduced with permission from BMJ Publishing Group Ltd.)

methods [52] (Table 8.2). The uniform drawback of the current formulations is that they do not cross the blood-brain barrier or effectively penetrate many tissues, and thus do not affect central nervous system pathology and have variable effects on other organ systems. Improvements in organ systems pathology are mixed; for the cardiac pathologies, it is generally acknowledged that long-term ERT reduces or at least stabilizes LV mass index, septal hypertrophy, and ejection fraction in MPS I, II, IV, and VI in most studies. The valvular abnormalities are not improved [53]. Coronary artery pathology improvement has not been specifically addressed, but there are case reports of sudden unexpected death from coronary artery stenosis in ERT-treated patients. For other pertinent systems, although there have been a few reports of improved obstructive sleep apnea, coarseness of facial features, and respiratory infections with ERT, studies have not yet demonstrated a reduction in adenoidal or tonsillar hypertrophy. Another therapy for MPS disorders has been hematopoietic stem cell transplant, which has shown promise in MPS I, but with mixed results in MPS II, III, IV, and VI. The overall message for the anesthesiologist caring for MPS patients is that each patient requires very careful multisystem evaluation, and because of variable outcomes, patients receiving ERT or who have had stem cell transplants should not be assumed to have significant improvement because these therapies do not appear to be consistently effective in reversing already established pathology even though they may prevent progression of the disease.

ERT is available for Pompe disease, but not for Danon disease; a review of ERT for infantile-onset Pompe disease showed that ERT markedly extended overall survival and ventilation-free survival, and also improved cardiomyopathy [54]. ERT can also stabilize late-onset Pompe disease but is not a cure for this condition. Gene therapy for this disease is being proposed as a better alternative given these mixed results of ERT after more than 10 years of use [55].

Aortopathy syndromes

Hereditary aortopathy syndromes are a group of disorders resulting in thoracic aortic aneurysms, and are generally divided into syndromic (Marfan Syndrome, Loeys-Dietz Syndrome, Ehlers-Danlos Syndrome) and familial non-syndromic thoracic aortic aneurysms [56]. The section will discuss the syndromic conditions, which are most commonly encountered by congenital cardiovascular anesthesiologist.

Marfan syndrome

Marfan syndrome is an autosomal dominant disorder with a mutation in the fibrillin 1 (FBN-1) gene on chromosome 15 (15q21.1) responsible for most cases, although more than 1,000 individual mutations in this gene have been associated with the syndrome[57]. Transforming growth

Table 8.2 Classification of mucopolysaccharidoses with enzyme replacement therapies

Type	Syndrome	Phenotype MIM number (#)	Deficient Enzyme (EC Classification)	Gene symbol	Affected GAGs	Inheritance	Recombinant enzyme	Brand name
MPSIH H/S S	Hurler Hurler/ Scheie Scheie	607,014- 607,015- 607,016	Alpha-L-iduronidase (3.2.1.76)	IDUA	DS, HS	AR	Laronidase	Aldurazyme®
MPSII	Hunter	309,900	Iduronate 2-sulfatase (3.1.6.13)	IDS	DS, HS	XL	Idursulfase alfa Idursulfase beta	Elaprase® Hunterase®
MPSIVA	Morquio A	253,000	Galactosamine-6-sulfatase (3.1.6.4)	GALNS	KS, CS	AR	Elosulfase	Vimizim®
MPSVI	Maroteax-Lamy	253,200	Arylsulfatase B (3.1.6.12)	ARSB	DS	AR	Galsulfase	Naglazyme®
MPSVII	Sly	253,220	Beta-glucuronidase (3.2.1.31)	GUSB	DS, HS, CS	AR	Vestronidase	Mepsevii®

Classification of mucopolysaccharidoses (MPSs) with types, syndromes' names, phenotype Mendelian Inheritance in Man (MIM) number (#), deficient enzymes with their Enzyme Commission (E.C.) classification, gene symbol, affected glycosaminoglycans (GAGs) (DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate; CS, chondroitin sulfate) inheritance (AR, autosomal recessive; XL, X-linked), names of recombinant enzymes and their commercial name. Data obtained from Online Mendelian Inheritance in Man (OMIM) https://www.ncbi.nlm.nih.gov/omim. Accessed on 7 April 2020.
Source: Parini and Deodato [52] / MDPI / CC BY 4.0.

factor-beta (TGF-beta) receptors 1 and 2 are also involved. Approximately 75% of patients with Marfan Syndrome have an affected parent and 25% are *de novo* mutations, and the prevalence is estimated to be between 1 : 5,000 and 1 : 10,000 with both genders equally represented. Fibrillin-1 is a glycoprotein that makes up the main constituent of the microfibrils of the extracellular matrix in multiple organs. The cardinal clinical features of this syndrome are aortic root aneurysms and ectopia lentis, with mitral valve prolapse another common clinical feature. Aortic dissection and rupture is the major cause of early morbidity and mortality in Marfan Syndrome, with the risk increasing significantly during adolescence, with death in up to 50% of undiagnosed patients by age 40 [58]. Skeletal features include kyphoscoliosis, pectus carinatum, tall stature, foot abnormalities, long fingers, and facial features such as malar hypoplasia and retrognathia. Dural ectasia is also frequently seen in Marfan Syndrome. Diagnosis is made by applying a scoring system known as the revised Ghent criteria (Table 8.3), and genetic testing for the fibrillin 1 gene.

Medical management of Marfan Syndrome consists of medications to control blood pressure, heart rate, and myocardial contractility to prevent aneurysm progression and usually include a beta blocker such as atenolol, and an angiotensin receptor blocker such as losartan. In addition to cardiac surgery for aortic root aneurysm and mitral valve prolapse, Marfan syndrome patients may need anesthetic care for eye surgery, spine surgery, and other orthopedic surgeries, as well as repeated imaging studies for assessment of the aortic root. In rare cases, Marfan Syndrome can present in infancy as Infantile Marfan Syndrome, with aortic root dilation as the major feature [59].

Table 8.3 Revised Ghent criteria for the diagnosis of Marfan syndrome

Criteria for diagnosis of MFS
In the absence of a family history of MFS:
1. Aortic root Z score ≥2 AND ectopia lentis
2. Aortic root Z score ≥2 AND an *FBNI* mutation
3. Aortic root Z score ≥2 AND a systemic score[a] ≥7
4. Ectopia lends AND an *FBNI* mutation with a known aortic pathological abnormality
In the presence of a family history of MFS (as defined above):
1. Ectopia lends
2. Systemic score[a] ≥7
3. Aortic root Z score ≥2

Source: Castellano et al. [58]. Reproduced with permission from SAGE Publications.

MFS, Marfan syndrome; FBNI, fibrillin-I.

[a] Points for systemic score: wrist AND thumb sign = 3 (wrist OR thumb sign = I); pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = I); hindfoot deformity = 2 (plain pes planus = I); dural ectasia = 2; protrusio acetabuli = 2; reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis = I; scoliosis or thoracolumbar kyphosis = I; reduced elbow extension = I; facial features (3/5) = I (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia); skin striae = I; myopia > 3 diopters = I; mitral valve prolapse = I.

Loeys-Dietz syndrome

Loeys-Dietz syndrome (LDS) is also an autosomal dominant connective tissue disorder characterized by aortic aneurysms, arterial tortuosity, hypertelorism, and bifid uvula or cleft palate that was described in 2005 [60]. Other clinical features include joint laxity, pectus deformity, dural ectasia, cervical spine abnormalities, and scoliosis. Four genetic mutations are associated with this disease, including TGF-beta receptors I and II, TGF-beta ligand gene and the SMAD3 gene. The most important feature of this disorder is widespread arterial involvement, with vascular tortuosity, a high risk of aneurysms and dissections throughout the arterial tree, and an aggressive vascular course. Aortic root aneurysms are even more common and severe than in Marfan Syndrome. There are no specific clinical criteria; the diagnosis is confirmed by molecular test, with arterial aneurysm or dissection, and a family history of the disorder being sufficient features. Medical therapy for prevention/slowing of aortic aneurysm growth is similar to Marfan Syndrome. In a case series of 79 patients with LDS and 256 with Marfan syndrome, 16% of LDS patients' initial presentation was acute aortic dissection, compared with 10% in the Marfan Syndrome group. The need for subsequent aortic surgery in LDS was 10–20 times greater with LDS than in Marfan Syndrome, ranging from 5 to 12%, and late mortality after aortic arch surgery in LDS was 33% [61]. Pregnancy in LDS has been associated with significant morbidity and mortality from an aortic dissection, but successful pregnancies and even cardiac surgery during pregnancy have been described with careful management plans [62].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders, with all subtypes exhibiting joint hypermobility, skin hyperextensibility, and tissue fragility. Up to 25% of EDS patients have aortic aneurysms. There are many forms of EDS, and recently they have been categorized by six different groups, each with several subtypes. The classic and hypermobile forms account for over 90% of the cases. Mutations in multiple genes have been implicated in this disorder, encoding collagen fibrils or proteins involved in the processing of these collagens [63] (Table 8.1).

See Chapter 31 for additional discussion of aortopathy syndromes and cardiac surgical and anesthetic approaches.

VACTERL association

VATER association was first described in the early 1970s. The term "association" was used because it was a co-occurrence of a group of congenital anomalies that was more than random. The original VATER malformations included **V**ertebral defects, **A**nal atresia, **T**racheoesophageal fistula with esophageal atresia, and **R**adial and **R**enal dysplasia. Later, the association became known as VACTERL; **V**ascular anomalies including single umbilical artery, **C**ardiac defects, and **L**imb abnormalities beyond radial were the added congenital malformations [64] (Figure 8.9). The incidence of the VACTERL association is between 1/10,000 and 1/40,000. This large range is due to the difficulty in "diagnosing"

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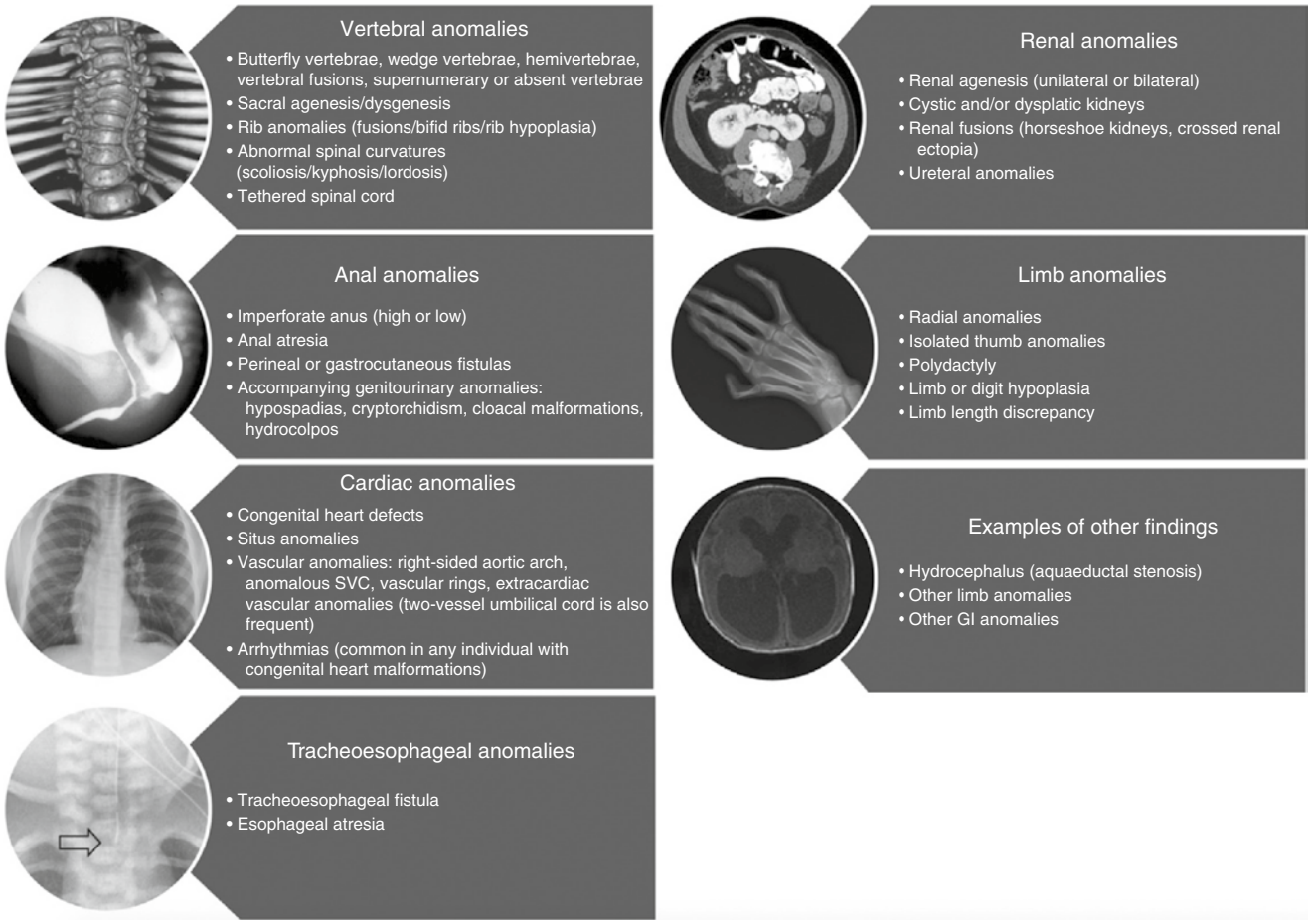


Figure 8.9 Examples of findings in the VACTERL association. The images in the circles represent radiological examples. Vertebral anomalies: 3D CT reconstruction showing thoracic segmentation anomalies; anal anomalies: contrast imaging showing rectoprostatic urethral fistula in a patient with ano-rectal malformations (ARMs); cardiac anomalies: chest radiograph showing midline heart in a patient with situs anomalies as part of the VACTERL association; tracheo-esophageal anomalies: radiograph showing the position of feeding tube placement (arrow) due to a tracheal pouch; renal anomalies: axial view from an abdominal CT showing horseshoe kidney; limb anomalies: skeletal anomalies affecting the radius, wrist, and thumb; examples of other findings: axial view from brain MRI showing hydrocephalus (due to aqueductal stenosis). GI, gastrointestinal; SVC, superior vena cava. (Source: Solomon et al. [31]. Reproduced with permission from Elsevier.)

patients with the association. Most agree that the presence of ≥3 malformations is required, but there is no genetic or diagnostic test for VACTERL. In fact, there is no one unifying cause for VACTERL. There are some cases or clusters in which there appears to be a genetic basis, although signaling pathways including Hedgehog, FGF, and NOTCH have been implicated, as well as environmental contributions [65, 66].

VACTERL may be suspected prenatally due to ultrasound findings including polyhydramnios or an absent gastric bubble suggestive of tracheoesophageal fistula/esophageal atresia (TEF/EA), colonic distension is suggestive of anal atresia, a single umbilical artery, renal and bony (vertebral, radial) abnormalities. After birth, inability to pass an oro- or nasogastric tube suggests TEF/EA, examination may suggest anal atresia, a single umbilical artery, cardiac and limb abnormalities. Patients with TEF/EA, anal atresia, single umbilical artery, or limb abnormalities should be considered at risk for VACTERL, and an echocardiogram should be performed. Of note, many other syndromes are associated with these malformations. For this reason, genetic testing should be undertaken. In addition, if patients have malformations that are not typical of VACTERL, this suggests that the patient may have a syndrome with overlapping features [65].

Vertebral abnormalities are present in 60–80% of patients with VACTERL and may include segmentation defects such as hemi-, butterfly, and wedge vertebrae. Other vertebral abnormalities include fusions and extra or missing vertebrae. These vertebral findings may be asymptomatic and picked up on radiological studies or they may cause symptoms that need to be addressed medically or surgically.

Imperforate anus, anal atresia, or anorectal malformations are present in 55–90% of patients with VACTERL. These may be detected during the newborn examination while trying to measure rectal temperature, or later with obstruction. In the first few days of life, a colostomy may be necessary with definitive surgical management occurring 1–2 months later [67].

Cardiac defects are often found in patients with VACTERL. Cunningham et al. reported that congenital heart defects were found in 67% of the patients in the study with ventricular septal defect being present in 58% of the patients with a

cardiac lesion. The congenital heart lesions ranged from the presence of persistent left superior vena cava or bicuspid aortic valve to lesions requiring repair or palliation in the neonatal period [68].

Tracheoesophageal fistula (TEF) with/without esophageal atresia is present in 50–80% of patients with VACTERL. Polyhydramnios or the absence of a gastric bubble on prenatal ultrasound may suggest the possibility of TEF. Postnatally, the inability to pass an oro- or nasogastric tube or choking with feeds may lead to the diagnosis. Surgery is generally necessary for the first days of life.

Renal anomalies may include unilateral agenesis, horseshoe kidney, and cystic or dysplastic kidneys. These may lead to decreased renal function. Limb malformations were originally confined to radial abnormalities, and these were found in approximately 50% of patients. Further characterization has led to the inclusion of lower limb anomalies and polydactyly [65].

Patients with VACTERL association may need surgical procedures in the first few days of life, most commonly a colostomy for anal atresia or a tracheoesophageal atresia repair. As the patient may not carry the diagnosis of VACTERL, one must consider the possibility of a coexisting cardiac lesion, and an echocardiogram should be performed. In addition, when a newborn patient presents to the neonatal or cardiovascular intensive care unit after birth, one must consider the possibility that other malformations including TEF/EA may exist [2]. A careful examination should be done. Patients presenting for cardiac surgery may have had a TEF/EA repair previously. Intraoperative transesophageal echocardiography may be contraindicated in these patients; epicardial echocardiography may be considered. Limb malformations, especially radial anomalies, may be associated with the difference in vascular anatomy. An ultrasound examination prior to line placement may be helpful. Renal anomalies should alert the perioperative team to the potential for preoperative or postoperative renal insufficiency. Markers of renal function should be analyzed pre-and postoperatively.

CHARGE syndrome

CHARGE syndrome was first described as an association of congenital anomalies in 1979, and the CHARGE acronym was coined in 1981: **C**oloboma, **H**eart defect, choanal **A**tresia, growth and developmental **R**etardation, **G**enital hypoplasia, and **E**ar anomalies/deafness. In 2004, Vissers et al. identified that a loss of function in the CHD7 gene (Chromodomain Helicase DNA-binding protein 7) located on chromosome 8q12 was associated with the syndrome. The mutation in the CHD7 gene was found to almost always be de novo, with rare occurrences of autosomal dominant inheritance [69]. However, CHARGE syndrome is still usually a clinical diagnosis based on the presence of major and minor phenotypic criteria. Some clinical features of the CHARGE syndrome are illustrated in Figure 8.10 [70].

The majority of patients have ocular abnormalities, most often coloboma. Coloboma can be associated with a variable reduction in visual acuity depending on the type of coloboma (iris, retina, choroid, etc.), with the chorioretinal coloboma being most common. Other ocular abnormalities may include microphthalmia, microcornea, cataracts, strabismus, ptosis, and refractive errors [70] (Table 8.4).

Congenital heart disease is reported in 75–80% of patients with CHARGE syndrome [71]. The type of defect varies, but there is a relative overrepresentation of conotruncal anomalies, atrioventricular septal defects, and septal defects [72]. Tetralogy of Fallot is the most common cyanotic defect associated with the syndrome [71].

Choanal atresia and other upper respiratory tract abnormalities are very common in patients with CHARGE syndrome. In 65% of patients, choanal atresia is noted after birth. Other causes of airway obstruction in these patients include subglottic stenosis and laryngotracheomalacia. Of note, 15–20% of these patients have cleft lip or palate, and 15–20% have tracheoesophageal fistula [70, 73] Obstructive sleep apnea is also very common. Abnormalities in growth and development may also be present, and patients may exhibit varying degrees of intellectual ability. Genital hypoplasia, especially in males, is a feature of the syndrome, and renal anomalies may also be present.

Outer ear abnormalities are very common in patients with CHARGE syndrome and can alert the care team to the possibility of the syndrome. The most common inner ear abnormality is the absence of the lateral semicircular canals, although other abnormalities are common. Most result in some sensorineural hearing loss or poor balance [70]. Cranial nerve dysfunction is also common in patients with CHARGE syndrome. Anosmia is almost always present. Cranial nerve dysfunction can lead to poor oromotor function, difficulty in swallowing, reflux, and aspiration. Endocrine issues may include hypothyroidism and hypocortisolism. Immunodeficiency can also be encountered. Some patients are athymic, and atypical severe combined immunodeficiency syndrome (SCID) may be present. This may result in increased susceptibility to infection [70].

Patients with CHARGE syndrome have congenital abnormalities spanning multiple organ systems. They are often medically complex, requiring multiple procedures and surgeries, including tracheoesophageal fistula repair, choanal atresia repair, congenital heart surgery, gastrostomy tube placement, fundoplication, tracheostomy, myringotomy tube placement, cochlear implants, direct laryngoscopy and bronchoscopy, diagnostic imaging procedures, and others. Anesthetic care may be challenging due to multiple congenital anomalies. Difficult intubation may be encountered due to respiratory tract abnormalities. Patients with feeding tubes may be susceptible to hypoglycemia while fasting. Patients with CHARGE syndrome have been reported to have a significant risk of postoperative airway events. These events were noted in 35% of general anesthetics, most commonly cardiac, gastrointestinal tract, and airway scope procedures. These events were most likely to occur in patients with feeding difficulties who had a gastrostomy tube or a fundoplication, implicating cranial nerve issues and difficulties managing secretions [74]. Postoperative obstruction due to adenotonsillar hypertrophy, secretions, and other airway abnormalities is also common. There are multiple reports of increased postoperative mortality, especially in the neonatal period [2, 75, 76]. Potential risk mitigation strategies include multidisciplinary planning, combining multiple procedures under one anesthetic, and having a healthy respect for cranial

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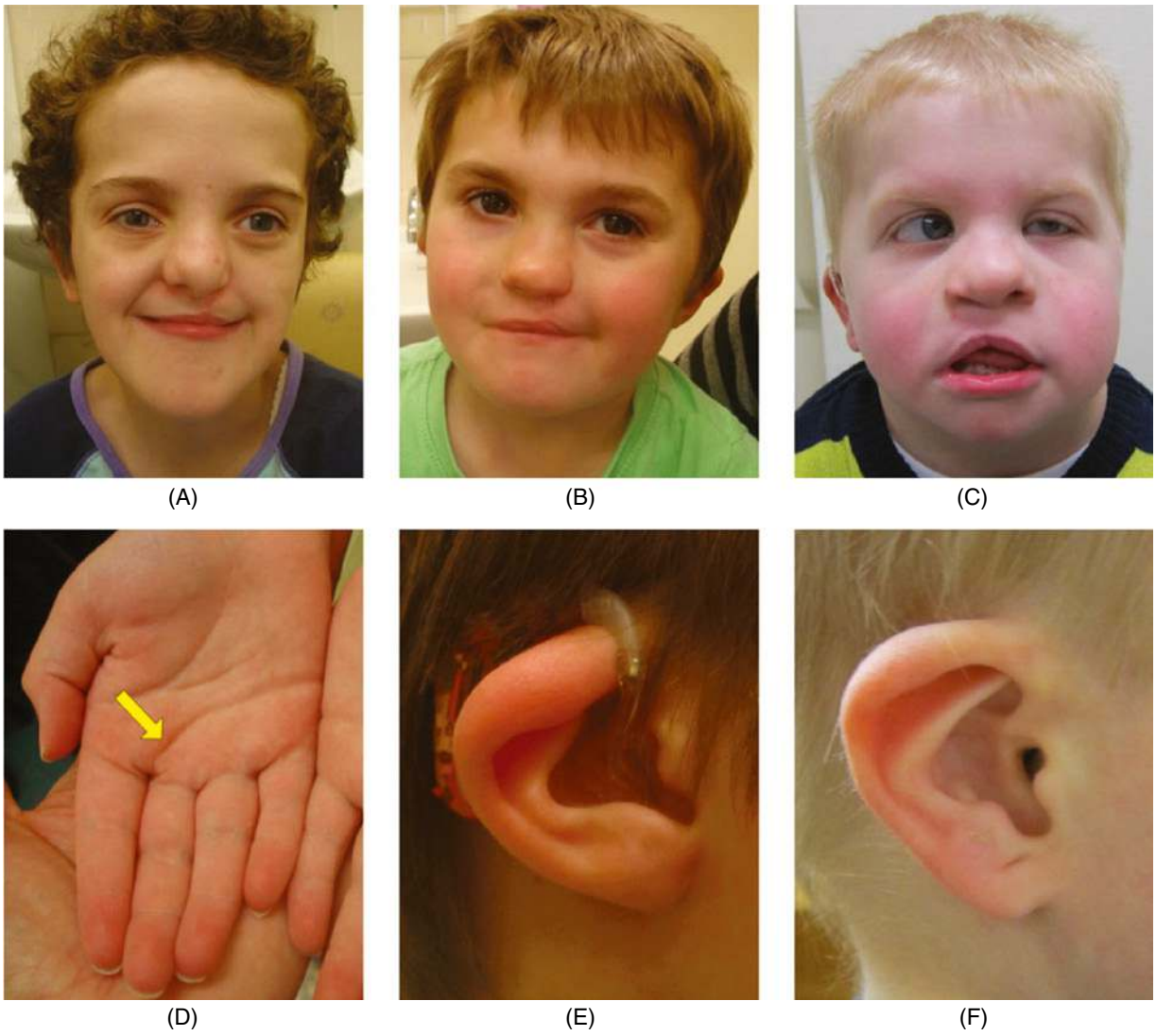


Figure 8.10 Clinical features of the CHARGE syndrome. (A) Cleft lip/palate repair, mild left facial palsy, and broad forehead in a 10-year-old girl. (B) Cleft lip/palate and square face with mild right facial palsy in a 6-year-old boy. (C) Left-sided microphthalmia, with prosthesis in situ, and a square face with broad forehead and broad nasal root in a 2.5-year-old boy. (D) "J"-shaped hockeystick palmar crease (yellow arrow). (E) Typical CHARGE ear with hypoplastic, overfolded helix and lobe, and a triangular concha. (F) Less typical appearing ear with a squared superior helix and crease on the lobe. (Source: Hsu et al. [35]. Reproduced with permission from John Wiley & Sons.)

nerve dysfunction, potential aspiration, and postoperative airway obstruction [2, 75, 76]. Due to these factors, early extubation after cardiac surgery may not be wise in patients with CHARGE syndrome. Refractory hypotension or failure to wean from cardiopulmonary bypass could be due to hypothyroidism or hypocortisolism in these patients. Treatment with liothyronine infusion or administration of a stress dose of hydrocortisone may be indicated.

Heterotaxy syndrome

Heterotaxy syndrome is a fascinating collection of disorders of left-right sidedness of multiple visceral organs; because the heart is the first organ to express laterality early in gestation, abnormalities of cardiac situs are very frequent in this syndrome, occurring in 75% or more of these patients [77]. Other findings are intestinal malrotation in about 70%, abnormalities of pulmonary situs in a similar percentage, and abnormal situs of the stomach, spleen, and liver in a high percentage, including asplenia and polysplenia. Heterotaxy syndrome may be seen in up to 3–7% of CHD patients and is estimated to occur in 1 : 5,000 to 10,000 live births. Many heterotaxy patients have single ventricle lesions, and heterotaxy syndrome can be broadly separated into asplenia and polysplenia patients. The asplenic patients have more than 50% incidence of single ventricle lesions, with total anomalous pulmonary venous return common as well. Abnormalities of systemic venous return are very common, including bilateral superior vena cavae, or interrupted inferior vena cavae. Patients with right atrial isomerism have bilateral right atria and often have bilateral sinoatrial nodes; conversely, those with left atrial isomerism often have no sinoatrial node. A classification scheme dividing heterotaxy syndrome into

Table 8.4 Phenotypic features of the CHARGE syndrome

Features	Details	Frequency
Coloboma	Iris, retina, choroid, disk, or microphthalmia	75–90%
Choanal atresia/stenosis	Unilateral or bilateral, bony or membranous	65%
Cranial nerve anomalies	Facial nerve palsy, auditory, vestibular, or vagal (swallowing problems)	Facial: 50–90%
	CNS abnormalities can also involve arhinencephaly, holoprosencephaly spectrum, or forebrain and hindbrain abnormalities	CNS abnormalities 55–85%
Characteristic ear anomalies	Outer ear tends to be symmetrically misshapen, low set, anteverted, cup-shaped, and wide with reduced vertical height	Outer ear 95–100%
	Triangular concha is a common finding	Inner ear: 90%
	Microtia, hypoplasia of the auditory canal, and preauricular tags can also be seen	
	Middle: ossicular malformation	
	Cochlear: Mondini defect	
	Temporal: absent/hypoplastic semicircular canals; highly predictive of the presence of a *CHD7* mutation	
Genital hypoplasia	Males: micropenis/cryptorchidism	50–70%
	Females: hypoplastic labia	
	Delayed puberty	
Developmental delay	IQ <70 is present in over 70%	70%
Cardiovascular malformation	Usually conotruncal, AV canal, and aortic arch abnormalities	50–85%
Growth deficiency	Hypothalamo-hypophyseal dysfunction leading to short stature and pubertal delay	70–80%
	Often birth centiles are low normal, around the 10th centile	
Orofacial cleft	Cleft lip/palate	15–20%
Distinctive facial features	Square face, prominent forehead, prominent nasal bridge and columella, and flat midface	NA
Additional features	Omphalocele/umbilical hernia	NA
	Bony scoliosis/hemivertebrae	
	Renal anomalies: dysgenesis or horseshoe/ectopic kidney	
	Hand and limb anomalies in 37%: polydactyly, J-shaped 'hockey stick' palmar flexion crease	
	Short neck, sloping shoulders, and nipple anomalies	
	Immune deficiency	

AV, atrioventricular; CNS, central nervous system; IQ, intelligence quotient; NA, not applicable.
Source: Hsu et al. [35]. Reproduced with permission from John Wiley & Sons.

isomerism of the left vs. right atrium is displayed in Table 8.5. indicating the major differences between these groups [78]. Because of these anatomic abnormalities of the conduction system, arrhythmias are very frequent in heterotaxy syndrome, including bradycardia syndromes in left atrial isomerism and atrial tachycardia syndromes with right atrial isomerism. Many of these patients undergo staged single ventricle palliation; and require procedures to correct TAPVR, provide pulmonary blood flow, or limit pulmonary blood flow in the neonatal period. The systemic venous abnormalities make these procedures particularly challenging, and survival for cardiac surgery in patients with heterotaxy syndrome is consistently lower than for the same cardiac operation in patients without heterotaxy, particularly for total anomalous pulmonary venous connection (TAPVC) and univentricular pathway [79]. In a large single-institution series of 264 heterotaxy patients with CHD, the mortality rate was 40.2%, with a median follow-up of 10.2 years (range 1–31 years), with no significant improvement in recent birth eras vs. patients born 1985–1991. Additional detail about surgical and anesthetic management of the cardiac lesions in heterotaxy syndrome is presented in Chapter 30. These patients also may require abdominal surgery for complications of intestinal malrotation.

The genetics of heterotaxy syndrome are complex and heterogeneous in both phenotype and genotype, with most cases appearing sporadically, and without disease history, and so suggesting de novo gene variants contribute [47, 80]. Abnormalities in the genes that determine cilia motility are involved in some heterotaxy cases. Cilia are microtubule-based organelles protruding from the cell surface that if motile, result in extracellular fluid flow. If immotile, these cilia can act as important signaling nodes; signaling between these forms of cilia are instrumental in breaking left-right symmetry during organogenesis; abnormal cilia genotypes have been associated with heterotaxy, and up to 40% of patients with heterotaxy have an abnormal respiratory ciliary function, leading to frequent respiratory complications. Patients with asplenia often have an abnormal immunologic function, but it is not always possible to assume even patients with polysplenia have normal immune systems, and so most of these patients are treated

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Table 8.5 Synopsis of cardiac and noncardiac anomalies in heterotaxy syndrome

Morphological features	Isomerism of left atrial appendage	Isomerism of right atrial appendage
Heart position	Any position (Dextrocardia, Mesocardia, Levocardia) Abnormal cardiac positions are common in 40–50% of patients.	Abnormal cardiac positions are more common in IRAA patients than the normal population.
Systemic veins	Interrupted IVC with azygos venous system continuation to SVC. Hepatic veins, isolated or in confluence drain into either of the atria. Bilateral SVC: Found in 40 % of cases and absent coronary sinus in 30–55% cases.	IVC drains into one of the atria. Hepatic veins may drain separately in the contralateral atrium (morphological representation of duplication of IVC). Bilateral SVC: Found in 50–60% cases and absent coronary sinus in 78% cases.
Pulmonary veins	PAPVC in >50% patients due to bilateral atrial connection of ipsilateral PVs or due to mal-aligned septum. Less frequently. TAPVC or TAPVD can be seen (10–12%). Scimitar syndrome in 1%.	Obstructed TAPVC is a common finding in >50% cases. Unobstructed TAPVC can also be present.
Atrial appendage	Both atrial appendages are of left atrial morphology (See text)	Both atrial appendages are of right atrial morphology (see text)
Atrial septum/Atrio-ventricular junction/valve	Partial AVSD, ostium primum ASD with two distinct AV orifices and cleft in left component of AV valve is common.	Common AV valve associated with complete AVSD or common atrium is frequently seen.
Univentricular AV connection	Less common (10–40%)	More common (more than 70%)
Outflow obstruction	Right outflow obstruction: less than 40%; Left ventricular outflow obstructions are seen more frequently (<50%) than IRA A.	Pulmonary stenosis/Atresia are common (>80%)
VA connection	The VA connection can be abnormal (TGA, DORV or single outlet) in around 50% of cases.	Abnormal ventriculo-arterial connection (single outlet, TGA, DORV) are more common (90–96%)
Significant CHD	Less frequent	>98%
Conduction system	Bilateral absence of sinus node may lead to bradyarrhythmias.	Two sinus nodes. The atrial tachyarrhythmias are common.
Lungs and bronchi	Bilateral morphological left bronchus and left lung rally (90%). Congenital lobar pneumonia and Scimital syndrome can be seen in few cases.	Bilateral morphological right bronchus and right lung (trilobed) (90%).
Spleen	Multiple spleens are commonly seen. In 5–10% cases, it may be absent or present singularly. Functional abnormalities are common.	The absence of a spleen is expected in this group. But in 10–15% of cases it may be present as a single or multiple masses. The spleen may be functionally abnormal.
Liver and stomach	Central liver is common in >70% cases. It may be asymmetrical, right or left-sided in few cases. The stomach may be central, right or left sided.	The majority patients have central liver. The stomach can be central, right or left.
Bowel malrotation and other abnormalities	Common in ILAA group.	Less frequent in this group
Pancreas	Not rare	Rare
Gall bladder	Common	Not reported in the literature

ASD, Atrial septal defect; AV, Atrio-ventricular; AVSD, Atrio-ventricular septal defect; CHD: Congenital heart disease; DORV: Double outlet right ventricle; ILA A, isomerism of left atrial appendage; IRA A, isomerism of right atrial appendage; IVC: Inferior vena cava; LVOTO: Left ventricular outflow tract obstruction; PAPVC: Partial anomalous pulmonary venous connection; PS/PA: Pulmonary stenosis or atresia; PV: Pulmonary valve; SVC: Superior vena cava; TAPVC/D: Total anomalous pulmonary venous connection/Drainage; TGA: Transposition of the great arteries; V-A (Concordance/Discordance), Ventriculo-Arterial (concordance or discordance).

Source: Mishra [78]. Reproduced with permission from Springer Nature.

with daily amoxicillin prophylaxis as well as targeted vaccination programs to prevent bacterial infections and sepsis [77].

Table of genetic syndromes and associations

Table 8.1. Displays the major cardiac genetic syndromes, with their major features, prevalence, gene defect, and cardiac and multisystem involvement including anesthetic considerations.

Genetic testing in CHD

Advances in both prenatal and postnatal genetic testing have prompted an earlier diagnosis of genetic syndromes in patients with congenital heart disease, which can inform prognosis, and assist the family and caregivers with therapeutic decision making. In addition, the genetic basis for CHD has seen an explosion of knowledge with advanced genetic testing. This section will review the most common genetic tests used in association with a CHD diagnosis. Prenatally, chorionic villus sampling between 10 and 13 weeks

gestation, or amniocentesis after 15 weeks can be offered; and blood testing postnatally can be sent [81]. With increasing utilization of genetic testing, these studies are now sent at any time in the life of a CHD patient, not just the neonatal period, i.e. children and adults often undergo testing, and parents may undergo testing to add data to help determine inheritance and risk of recurrence in future children. Because of the complexity of CHD genetics, an expert in cardiac genetics should guide the choice of testing modalities and their interpretations. Chapter 6 presents additional information about the genetics of cardiovascular development.

Chromosomal microarray (CMA)

Chromosomal microarray (CMA) compares patient deoxyribonucleic acid (DNA) to normal reference DNA to detect copy number variations (CNVs), which are DNA deletions and duplications on chromosomes. There are four different types of CMA studies with unique advantages and disadvantages, but for most indications in CHD patients, a comprehensive CMA is ordered, which includes both array comparative genomic hybridization and single nucleotide polymorphism techniques to assess the whole genome [82]. This test is considered the first-line evaluation for CHD patients with multiple congenital anomalies, developmental delay, or autism, and for all patients with major cardiovascular anomalies because of its high yield [83]. The main drawback for postnatal testing is a relatively long turnaround time of about 2 weeks; more rapid tests (see below) may be required for urgent clinical decision-making.

Fluorescence in-situ hybridization (FISH)

FISH and a similar test called multiplex ligation probe-dependent analysis are tests to detect copy number variations at specific regions, especially Trisomy 13, 18, 21, and sex chromosomes. The advantage of this approach is a more rapid turnaround time of 2–3 days, which can affect urgent management decisions in a neonate or unstable patient.

Chromosomal karyotype

A chromosomal karyotype is a visual inspection of all chromosomes to detect the number, i.e. trisomy and aneuploidy, and large structural anomalies like duplications or deletions, and banding patterns. This is an older test that is no longer recommended for multiple congenital anomalies in CHD patients.

Single gene sequencing

In diseases with known single-gene causes, this test determines the nucleotide sequence of the specified gene when one of these disorders is suspected. Turnaround time is 3–4 weeks.

Whole exome sequencing

Whole exome sequencing (WES) is a newer, large-scale sequencing technology that determines the nucleotide sequences of all of the protein-encoding regions of the entire genome, the exons. Analysis of this data is complex and depends significantly on the clinical information provided to focus the report on the relevant findings. This testing can also report incidental findings, and variants of unknown significance, i.e. not associated with a known disorder, which require family counseling about these results. This test is best for the assessment of multiple possible single-gene disorders simultaneously in a patient with a complex phenotype. Turnaround time is 3–4 months.

Panels of tests have been developed for specific diseases and related entities; Tables 8.6 and 8.7 display the approach utilized at Texas Children's Hospital.

Table 8.6 Recommended genetic testing by the lesion

Left-sided lesions	
HLHS	Male: CMA Female: CMA and rapid FISH for sex chromosomes to screen for Turner syndrome (if outside the newborn period or non-urgent, do only CMA) If CMA negative, with any of the following: renal anomalies, hypotonia, ear anomalies: consider Kabuki panel (may also do WES)
Coarctation of the aorta, moderate-to-severe aortic stenosis	CMA If CMA negative, with any of the following: renal anomalies, hypotonia, ear anomalies: consider Kabuki panel (may also do WES)
BAV in a female with any of the following: coarctation, PAPVR, LSVC, absent ductus arteriosus, cystic hygroma, lymphedema, shield chest, short stature, webbed neck	Karyotype
Supravalvar aortic stenosis	CMA If CMA negative, elastin gene (*ELN*) sequencing with deletion/duplication testing
Right-sided lesions	
Pulmonary stenosis with any of the following: hypertrophic cardiomyopathy, conduction abnormalities, fetal chylous effusions, short stature, webbed neck, shield chest, developmental delay, cryptorchidism, dysmorphic features	Noonan panel
Conotruncal defects	
TOF (PS or PA-VSD)	CMA If seen with bile duct paucity, cholestasis, butterfly vertebrae, ocular anomalies, growth delay, hearing loss, horseshoe kidney: also do *JAG1* and *NOTCH2* gene sequencing (or CHD panel that includes these)
Truncus arteriosus, DORV, IAA with VSD	CMA
Right aortic arch (even if isolated)	CMA

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Table 8.6 (Continued)

Aortic disease	
Aortic root dilation without CHD and features concerning for Marfan-like disorder	Aortopathy panel
Ascending aortic dilation with lung disease and/or pulmonary hypertension	Aortopathy panel
Others	
AVSD	Features suggestive of T21: karyotype (unless diagnosis critical, then rapid FISH for chromosome 21) No concerning facial features, or features not consistent with T21: CMA (will also detect T21) With short stature, conduction abnormalities, hypertrophic cardiomyopathy, webbed neck, shield chest, developmental delay, cryptorchidism, abnormal facies: consider Noonan panel
Heterotaxy	CMA and heterotaxy panel
All other CHD with the exception of isolated muscular VSDs, nonsyndromic isolated ASDs, isolated BAV, isolated LSVC	CMA

ASD, atrial septal defect; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; CHD, congenital heart disease; CMA, chromosomal microarray; DORV, double-outlet right ventricle; FISH, fluorescent in-situ hybridization; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; LSVC, left superior vena cava; PA, pulmonary atresia; PAPVR, partial anomalous pulmonary venous return; PS, pulmonary stenosis; T21, trisomy 21; TOF, tetralogy of Fallot; VSD, ventricular septal defect; WES: whole-exome sequencing.
Source: D'Alessandro et al. [82]. Reproduced with permission from Texas Children's Hospital.

Table 8.7 Recommended genetic testing by suspected diagnosis

Suspected diagnosis	**Testing**
Down syndrome	Karyotype If the diagnosis is critical in the newborn period, rapid FISH for chromosome 21 Will also be detected by CMA, but won't identify rearrangement, low-level mosaicism
Trisomy 13,18	Newborn rapid FISH for chromosome 13,18 *and* karyotype Will also be detected by CMA, but won't identify rearrangement, low-level mosaicism
Turner syndrome	With HLHS: rapid FISH for sex chromosomes If strongly suspect or to confirm the diagnosis: karyotype with FISH for Y centromere Will also be detected by CMA, but won't identify rearrangement, low-level mosaicism
Williams syndrome	Best: CMA Will also be detected with FISH for the Williams region If CMA negative or if family history of SVAS, strongly consider elastin gene (*ELN*) sequencing with deletion/duplication testing
22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)	Best: CMA Will also be detected with FISH for DiGeorge (usually includes chromosomes 22 and 10)
Noonan syndrome	Best: Noonan syndrome panel (adding deletion/duplication will diagnose an additional 5%) Will also be detected on WES
Marfan syndrome	Best: Aortopathy panel Will also be detected on WES
Loeys-Dietz syndrome	Best: Aortopathy panel Will also be detected on WES
Holt-Oram syndrome	TBX5 gene sequencing Will also be detected on WES and most CHD gene panels
Ehlers-Danlos syndrome	
• Hypermobile type (type 5)	There is no current diagnostic test (but there are clinical diagnostic criteria). If a personal history of easy bruising/bleeding, or abnormal skin (atrophic scars, poor wound healing, highly elastic), or family history of vascular/organ rupture, must exclude other types of EDS with EDS or aortopathy panel
• Vascular EDS (type 4)	Best: EDS panel (unless there is root dilation, then do aortopathy panel) Will also be detected on aortopathy panel or WES
• Classical EDS/ Classical-like EDS/ Cardiac-valvular EDS (types 1–3)	Best: EDS panel (unless there is root dilation, then do aortopathy panel) Will also be detected on aortopathy panel or WES
CHARGE syndrome	Best: CHD7 sequencing with deletion/duplication Will also be detected on WES

CHD, congenital heart disease; CMA, chromosomal microarray; EDS, Ehlers-Danlos syndrome; FISH, fluorescent in-situ hybridization; HLHS, hypoplastic left heart syndrome; SVAS, supravalvar aortic stenosis; WES, whole-exome sequencing.
Source: D'Alessandro et al. [82]. Reproduced with permission from Texas Children's Hospital.

Ethics in congenital heart disease

Ethical considerations for treatment

CHD patients with genetic syndromes often present with complex multisystem disease, in addition to congenital heart defects which may also be very complicated and may require multiple procedures for diagnosis and treatment in the catheterization laboratory and operating room. Long duration

ICU stays are necessary for some of these patients, and neurodevelopmental disabilities, either associated with the genetic syndrome, or because of neurological morbidity associated with the CHD itself or the treatment, occur in a significant proportion of these patients, with up to 25% syndromic patients with severe impairment, and 65% with mild or combined disability [84]. Knowledge about the genetics of CHD, and the prognosis for these patients, has expanded significantly as well. At the same time, surgical mortality for complex CHD continues to decrease, and the ability to treat complex lesions successfully with comprehensive multidisciplinary approaches to surgery, catheter intervention, and ICU care has increased so that patients who a decade ago would not be offered treatment, are now being offered these interventions. Cardiac surgery for Trisomy 13 and 18 patients (see above) is one example of this change [85]. Finally, the use of mechanical support, both as an acute intervention such as for ECMO-CPR (see Chapters 25 and 37) and failing to wean from bypass, and as a long-term bridge to transplant or even as destination therapy, has expanded greatly [86]. The ethical implications of this progress are profound, and the expectations and ethical perspectives of both providers and parents have great variability, and so it is crucially important that each institution have a clinical ethics program in place and a committee or team that can bring all the stakeholders together and provide consultation and advice in a multidisciplinary manner. Parents' understanding and perception of cardiac surgical risk vary greatly, and the relationships with the physicians involved in their child's care are crucial to establishing trust in times of critical decision-making [87]. In addition to the ICU team, interventional cardiologists and surgeons, the patient's primary cardiologist, and support for the family by social workers, clergy, or patient advocates are important. Trained, experienced ethicists who are objective parties not directly involved in the treatment of the patient are very important team members. Palliative care specialists are often involved in the care of these patients as well. The ethics consultation service should be utilized whenever there are significant questions or disagreements about a treatment course [88]. The parents and family need to be integrally involved in the process. Discussions about prognosis, outcome, the benefit of further treatment vs. risk of death, severe morbidity, or ongoing pain are very important for this group of patients. Although anesthesiologists are not always included in such discussions, as part of comprehensive multidisciplinary care, they should be involved as much as possible, particularly to add perspective about anesthetic risk and outcome, and ongoing pain from the procedures planned.

Palliative care in CHD

Palliative care is sometimes confused with hospice care, that provided at end of life to a patient with a terminal illness and limited life span, even by medical providers. Palliative care actually has a goal of improving the quality of life for patients and their families facing a life-threatening or life-limiting illness at any stage, not just the end of life, and the World Health Organization adds that for children, palliative care should begin with the diagnosis of a serious illness. An interdisciplinary team of physicians, nurses, chaplains, social workers, therapists, child life specialists, and others, is often involved. Palliative care objectives include defining goals of care, advance care planning, pain and symptom management, care coordination, and end of life assessment and management [89]. Palliative care in CHD can often start very early, even potentially in the prenatal period for some cardiac lesions. Involvement early in the neonatal period for genetic syndrome patients with critical heart disease can allow palliative care providers to establish a relationship with the parents and provide continuity between the obstetrical and pediatric environments and support short and long-term decision-making, in conjunction with treating physicians and other consultants [90]. For very high-risk patients, including some with multiple extracardiac anomalies, early discussion of goals of treatment can help avoid burdensome or futile interventions, start possible end-of-life discussions, and allow parallel planning depending on outcomes of procedures. Involving palliative care specialists can also promote better communication and acquisition of primary palliative care skills among intensivists, cardiologists, and surgeons, with the goal of a multidisciplinary team of experts unifying goals of comforting and curing.

The anesthesiologist can be involved in discussions about goals of care and contribute to discussions about providing pain relief and comfort. It is also important to understand goals for resuscitation and other invasive procedures during anesthetic care, and plan, with the parents, ICU team, and the patient when appropriate, what the treatment course will be in case of arrest or clinical deterioration. A question that often arises is whether a patient is a candidate for ECMO after a cardiac arrest. These issues should be clarified before providing the anesthetic, and the anesthesiologist should not assume that all orders that limit resuscitative efforts are automatically suspended during anesthetic care [91].

The increasing population of adult congenital heart disease patients is providing additional opportunities to engage palliative care specialists in planning, with the patient if intellectually able to understand and participate, their goals of care, advanced directives, and end of life planning. In a survey of 150 ACHD patients in the outpatient setting, 69% were willing to discuss advance care planning, 79% were willing to have a meeting to discuss their goals and care preferences, and 91% to speak to a clinician who specializes in palliative care [92].

Conclusions

With the high frequency of genetic syndromes with multisystem involvement in CHD, it is important for the anesthesiologist to have an understanding of the most common diagnoses to assist in planning for anesthetic care and in anticipating outcomes. This chapter has reviewed the genetic basis and clinical findings in the most common cardiac genetic syndromes. There are many additional, less common syndromes with cardiac involvement, and the reader is directed to comprehensive reference sources which can provide information about these rare patients [46–48, 93]. Finally, the anesthesiologist is a member of the multidisciplinary team providing expert, compassionate care to patients and families with these complex syndromes who often undergo multiple procedures, and should seek to be involved in clinical decision- making whenever possible.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Patel A, Costello JM, Backer CL, et al. Prevalence of non-cardiac and genetic abnormalities in neonates undergoing cardiac surgery: analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg 2016;102:1607–14. A large database review reporting a nearly 20% incidence of noncardiac anomaly, genetic abnormality, or syndrome in neonates undergoing cardiac surgery. The presence of these anomalies was associated with worse mortality in hypoplastic left heart syndrome and conotruncal anomalies.

11 Lewanda AF, Matisoff A, Revenis M, et al. Preoperative evaluation and comprehensive risk assessment for children with Down syndrome. Paediatr Anaesth 2016;26(4):356–62. A review article that presents a comprehensive review of Down syndrome and anesthesia, with emphasis on thorough multisystem evaluation and risk assessment.

27 Cooper DS, Riggs KW, Zafar F, et al. Cardiac surgery in patients with trisomy 13 and 18: an analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. J Am Heart Assoc 2019;8(13):e012349. A 2019 study of the Society of Thoracic Surgeons Congenital Heart Surgery Database of children with T13 and T18 who underwent cardiac surgery (2010–2017) demonstrated that while 70% of centers offered surgery on these patients, mortality remained high at 15% with a high rate of complications. Those who required preoperative mechanical ventilation had an 8 times increased risk of mortality.

30 Matisoff AJ, Olivieri L, Schwartz JM, Deutsch N. Risk assessment and anesthetic management of patients with Williams syndrome: a comprehensive review. Paediatr Anaesth 2015;25(12):1207–15. A comprehensive review of anesthesia risk assessment and management in patients with Williams Syndrome. Proposes a now widely-used risk stratification scheme for adverse events with anesthesia.

45 Braunlin EA, Harmatz PR, Scarpa M, et al. Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. J Inherit Metab Dis 2011;34:1183–97. A very well written comprehensive review of cardiac disease and outcomes in patients with mucoopolysaccharidoses.

58 Castellano JM, Silvay G, Castillo JG. Marfan syndrome: clinical, surgical, and anesthetic considerations. Semin Cardiothorac Vasc Anesth 2014;18(3):260–71. A thoughtful and thorough review of Marfan syndrome with excellent discussion of genetics and pathophysiology, and then a presentation of surgical and anesthetic considerations.

64 Solomon BD, Baker LA, Bear KA, et al. An approach to the identification of anomalies and etiologies in neonates with identified or suspected VACTERL (vertebral defects, anal atresia, tracheo-esophageal fistula with esophageal atresia, cardiac anomalies, renal anomalies, and limb anomalies) association. J Pediatr 2014;164(3):451–7.e1. A comprehensive review of VACTERL association, addressing all of the multiorgan involvement as well as the proposed genetic underpinnings of this condition.

70 Hsu P, Ma A, Wilson M, et al. CHARGE syndrome: A review. J Paediatr Child Health 2014;50:504–11. A review of CHARGE syndrome with excellent figures and tables as well as a clear presentation of the features, treatment, and outcomes of this complicated disorder.

78 Mishra S. Cardiac and non-cardiac abnormalities in heterotaxy syndrome. Ind J Pediatr 2015;82(12):1135–46. A comprehensive review of heterotaxy syndrome clinical findings, with excellent tables and figures to illustrate this heterogeneous condition.

90 Mazwi ML, Henner N, Kirsch R. The role of palliative care in critical congenital heart disease. Semin Perinatol 2017;41(2):128–32. An excellent introduction to the principles of palliative care for the patient with congenital heart disease.

CHAPTER 9

Physiology and Cellular Biology of the Developing Circulation

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Introduction

The circulatory system in congenital heart disease (CHD) continually changes and develops in response to both normal and pathologic stimuli. The response to anesthetic and surgical interventions must be understood in this framework and is often radically different from the usual, expected pediatric and adult situations with a "normal" cardiovascular system. This chapter will review developmental changes of the cardiovascular system from fetal life through to adulthood, in both the normal and pathophysiologic states associated with CHD. Not much is known about the development of the normal and diseased human heart. Much of the information discussed in this chapter was derived from animal models, and new information will undoubtedly be discovered as human myocardial tissue is studied.

Development from fetus to neonate

Circulatory pathways

The fetus receives oxygenated and nutrient-rich blood from the placenta via the umbilical vein and ejects desaturated blood through the umbilical arteries to the placenta, thus, the placenta, not the lung, serves as the organ of respiration. Blood flow largely bypasses the lungs *in utero*, accounting for only about 7% of the fetal combined ventricular output [1]. Pulmonary vascular resistance (PVR) is high, and the lungs are collapsed and filled with amniotic fluid. This forms the basis for fetal circulation, which is a parallel circulation, rather than the series circulation seen postnatally. Three fetal circulatory shunts exist to carry better-oxygenated blood from the umbilical vein to the systemic circulation: the ductus venosus, ductus arteriosus, and foramen ovale (Figure 9.1A) [2]. Approximately 50% of the umbilical venous blood, with an oxygen tension of about 30–35 mmHg, passes through the ductus venosus, and then goes into the right atrium. There it streams preferentially across the foramen ovale, guided by the valves of the sinus venosus and Chiari network into the left atrium. Thus, the brain and upper body preferentially receive this relatively well-oxygenated blood, which accounts for 20–30% of the combined ventricular output. Blood returning in the inferior vena cava represents about 70% of the total venous return to the heart, and two thirds of this deoxygenated blood passes into the right atrium and ventricle. About 90% of the blood flows through the ductus arteriosus to supply the lower fetal body.

After birth, there is a dramatic fall in PVR and an increase in pulmonary blood flow, with inflation and oxygenation of

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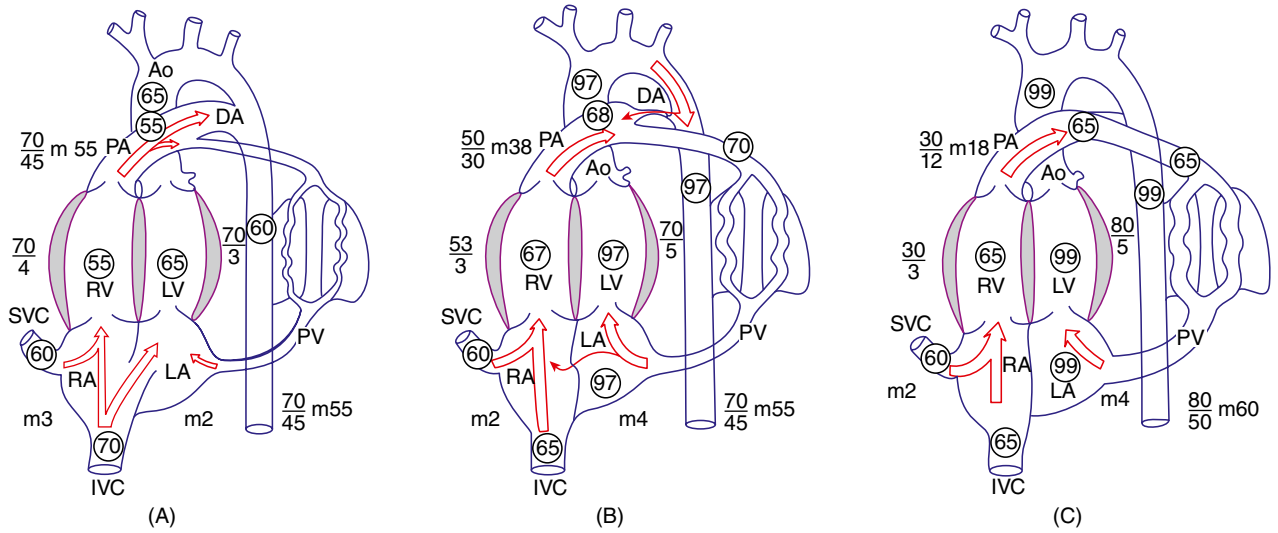


Figure 9.1 Transition from fetal to mature circulation. (A) Fetal circulation. (B) Transitional circulation. (C) Mature circulation. Circled numbers are oxygen saturations, uncircled numbers are pressures in mmHg. Ao, aorta; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; m, mean pressure; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava. (Source: Rudolph [2]. Reproduced with permission of John Wiley & Sons.)

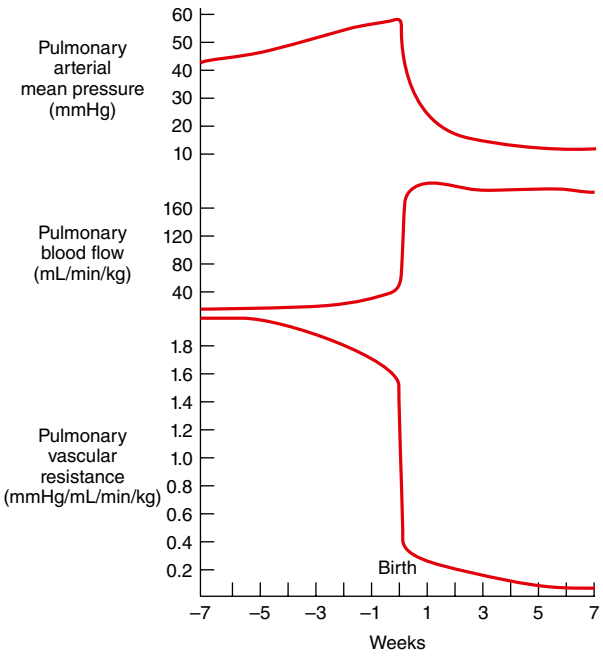


Figure 9.2 Changes in pulmonary artery pressure, pulmonary blood flow, and pulmonary vascular resistance in the lamb after birth. (Source: Rudolph [3]. Reproduced with permission of John Wiley & Sons.)

the lungs (Figure 9.2) [3]. The placental circulation is removed, and all of these changes lead to the closure of the ductus venosus, constriction of the ductus arteriosus, and reversal of pressure gradients in the left and right atria, leading to the closure of the foramen ovale. This leads to a state called the transitional circulation (Figure 9.1B), which is characterized by high pulmonary artery pressures and resistance (much lower than *in utero*, however), and a small amount of left-to-right flow through the ductus arteriosus. This is a labile state, and failure to maintain lower PVR can rapidly lead to reversion to fetal circulatory pathways, and right-to-left shunting at the ductus arteriosus and foramen ovale. This maintenance of fetal circulatory pathways is necessary for survival in many CHDs, particularly those dependent on a patent ductus arteriosus (PDA) for all or a significant portion of systemic or pulmonary blood flow, or atresia of atrioventricular valves. Maintenance of ductal patency with prostaglandin E1 (PGE_1) is crucial in these lesions. In a two-ventricle heart with large intracardiac shunts, maintenance of the fetal circulation leads to right-to-left shunting at the foramen and ductal levels, and thus hypoxia results. Conversion to the mature circulation (Figure 9.1C) in the normal heart occurs over a period of several weeks, as the PVR falls further, and the ductus arteriosus closes permanently by thrombosis, intimal proliferation, and fibrosis. Factors favoring the transition from fetal to mature circulation include normal oxygen tensions and physical expansion of the lungs, normal pH, nitric oxide, and prostacyclin. Factors favoring reversion to fetal circulation include low oxygen tension, acidotic pH, lung collapse, and inflammatory mediators (leukotrienes, thromboxane A2, platelet-activating factor) as seen in sepsis and other related conditions, and endothelin A receptor activators [4].

Myocardial contractility

The fetal myocardium is characterized by poorly organized cellular arrangements, and fewer myofibrils with a random orientation, in contrast to the parallel, well-organized myofibrillar arrangement of the adult myocardium [5] (see later in this chapter). Fetal hearts develop less tension per gram than adult hearts, because of increased water content and fewer contractile elements. Calcium cycling and

excitation-contraction coupling are also very different, with poorly organized T-tubules and immature sarcoplasmic reticulum, leading to more dependence on free cytosolic ionized calcium for normal contractility. Despite this immature state, the fetal heart can increase its stroke volume in a limited fashion up to left atrial pressures of 10–12 mmHg according to the Frank-Starling relationship, as long as afterload (i.e., arterial pressure) is kept low [6]. These features continue throughout the neonatal and early infancy periods.

KEY POINTS: DEVELOPMENT FROM FETUS TO NEONATE

- The transition from fetus to neonate involves a decrease in PVR, elevation of left heart pressures, and closure of shunts at the ductus arteriosus, foramen ovale, and ductus venosus.
- The transitional circulation is an intermediate state between fetal and adult circulation and may revert to fetal circulation with the persistence of hypoxemia, acidosis, CHD, or other conditions with elevated pulmonary artery pressures.
- The fetal heart develops less tension per gram of resistance than the mature heart and has limited ability to increase stroke volume up to left atrial pressure of only 10–12 mmHg.

Development from neonate to older infant and child

At birth, the neonatal heart must suddenly change from a parallel circulation to a series circulation, and the left ventricle, in particular, must adapt immediately to dramatically increased preload from blood returning from the lungs, and increased afterload as the placental circulation is removed. The very high oxygen consumption by the newborn necessitates a high cardiac output for the first few months of life. However, animal models have demonstrated that both the fetal and newborn myocardia develop less tension in response to increasing preload (sarcomere length), and that cardiac output increases less for the same degree of volume loading [7, 8] (Figure 9.3). Resting tension, however, is greater in the newborn than in the mature heart. This information suggests that the newborn heart is operating near the top of its Frank-Starling curve and that there is less reserve in response to both increased afterload and preload. This observation is borne out clinically in newborns (after complex heart surgery) who are often intolerant of even small increases in left atrial pressure or mean arterial pressure. The newborn myocardium also has only a limited ability to increase its inotropic state in response to exogenous catecholamines and is much more dependent on heart rate to maintain cardiac output than is the mature heart. One reason for this is the high levels of circulating endogenous catecholamines that appear after birth, which are necessary to make the transition to extrauterine life [9]. As these levels decrease in the weeks after birth, contractile reserve increases.

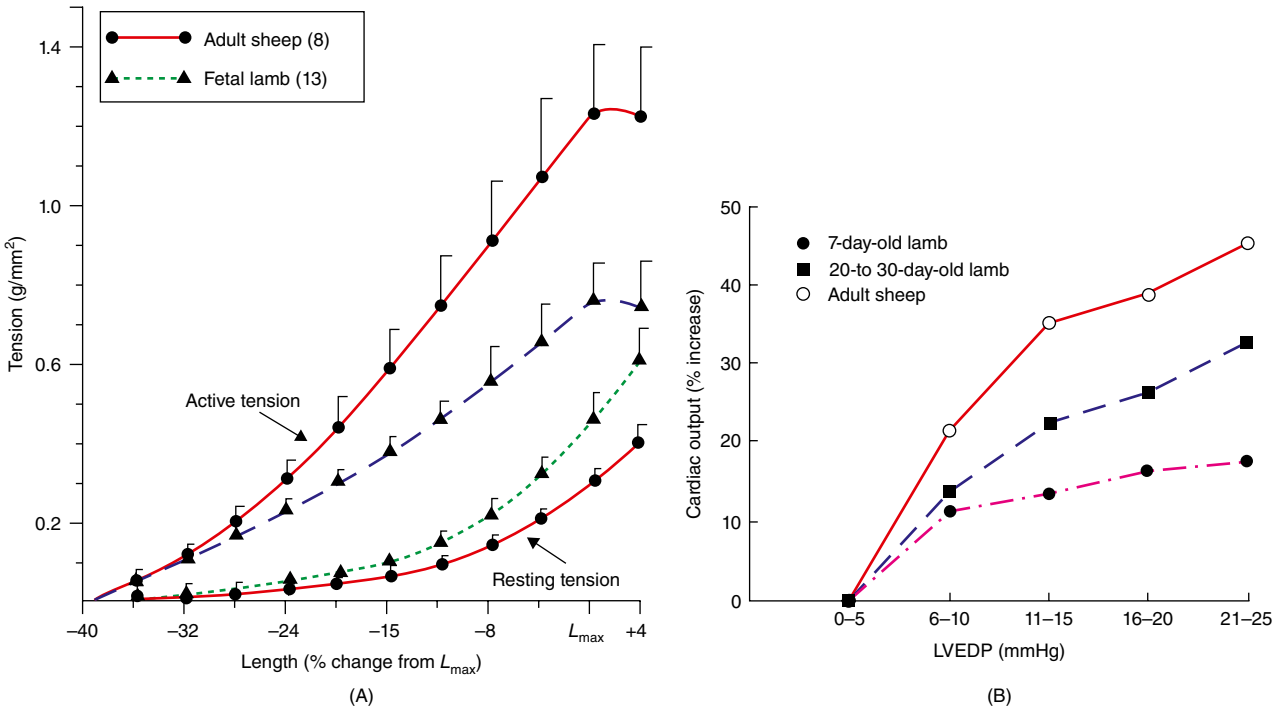


Figure 9.3 (A) Isometric resting and active length-tension relationships in fetal and adult lamb cardiac muscle strips. (Source: Friedman [7]. Reproduced with permission of Elsevier.) (B) Response to volume load of normal saline at 5 mL/kg/min, at constant heart rate. LVEDP, left ventricular end-diastolic pressure, Lmax, maximum muscle strip length. (Source: Friedman and George [8]. Reproduced with permission of Elsevier.)

The neonatal myocardium is less compliant than the mature myocardium, with increased resting tension as noted earlier, and a significantly greater increase in ventricular pressure with volume loading [10]. This implies that the diastolic function of the neonatal heart is also impaired compared with the mature heart [11]. The myofibrils of the newborn heart also appear to have a greater sensitivity to calcium, developing a greater tension than adult myofibrils when exposed to the same free Ca^{2+} concentration *in vitro* [12].

It must again be emphasized that nearly all of this data was obtained from animal models, and although the information appears to agree with what is observed clinically, there is a need for more non-invasive studies of normal human hearts from the neonatal period through adulthood to confirm these impressions of cardiac development.

Gene expression in cardiac development

Progress has been made recently in understanding the genetic aspects of human cardiac development, and in contrast to the physiologic studies which are almost exclusively performed in animal models, small amounts of human cardiac tissue obtained from biopsy or autopsy specimens can be used for these studies. Some aspects of these developmental changes will be reviewed.

Cardiomyocyte maturation begins after birth and is crucial for efficient contractility and metabolism. A hallmark of cardiomyocyte maturation is isoform switching of contractile genes from the fetal to the adult state [13]. Myosin is the major protein component of the thick filaments of the cardiac myofibril, and differences in the expression of this protein may play a significant role in myocardial contractility. Chromosome 14 has the genetic material responsible for producing the myosin heavy chain (MHC) which makes up the backbone of the thick filaments, and two major isoforms, namely α and ß, exist. The ß isoform predominates at birth but the α isoform becomes predominates through maturation [14]. The myosin light chain has multiple isoforms, and the relative proportions of these isoforms change with development, and also in response to pressure loading of the heart. The isoforms that predominate in the newborn myocardium appear to confer a greater sensitivity to Ca^{2+} than those seen in the mature heart [15] and may contribute to the increased sensitivity of the neonatal myocardium to Ca^{2+}.

Troponin I, C, and T are critical proteins that bind Ca^{2+} and regulate the interaction between myosin and actin, directly affecting the force of contraction. Troponin C, the Ca^{2+}-binding portion of the troponin moiety, does not change with development. Troponin I, however, has two major isoforms, a slow skeletal muscle type that predominates in the heart in fetal and neonatal life, and the cardiac isoform, which is the only isoform expressed in the mature heart [16]. Only the cardiac (mature) isoform responds to ß-adrenergic stimulation, producing a faster twitch development and greater twitch tension. However, contractility in the neonatal myofibrils containing the immature myosin light chain (MLC) isoform is more resistant to acidosis. Four isoforms of troponin T are expressed in the fetal and neonatal heart, but only one in the mature heart. These isoforms exhibit different levels of ATPase activity and Ca^{2+} sensitivity (see later), with greater ATPase activity and Ca^{2+} sensitivity seen in the immature forms [12]. Tropomyosin [17] has two isoforms and actin [18] has three isoforms, which are expressed in different proportions as developmental changes occur, but the functional significance of these changes has yet to be elucidated.

Some enzymes are affected by the loading conditions of the heart. Protein kinase C (PKC) is an enzyme with a major role in transmembrane signal transduction through phosphorylation of a number of downstream intracellular components (see the section on "Calcium cycling in the normal heart") [19]. There are six isoforms of this enzyme, and it is not affected during development. However, in aortic stenosis producing left ventricular hypertrophy, all isoforms except PKC-β are dramatically upregulated, and in dilated cardiomyopathy, there is a dramatic upregulation of PKC-β. Phosphodiesterase (PDE) is an enzyme involved in the termination of the action of cyclic adenosine monophosphate (cAMP), which regulates the contractile state of the myocardium (see later). Expression of the isoform PDE-5 is dramatically increased in the hypertrophied human right ventricle in patients with pulmonary hypertension, and inhibition of this enzyme improves ventricular contractility [20].

New information is available on the molecular and cellular basis for normal cardiac development and the causes of CHD [21]. A missense mutation in the myocardial protein actin has been discovered to be the cause of isolated secundum atrial septal defect in some patients [22]. Pluripotent cardiac progenitor cells reside in the human neonatal myocardium in relatively high numbers during the first month of life [23]. This knowledge has given rise to the exciting notion that these stem cells could potentially be used to facilitate recovery from cardiac morbidity or to enhance surgical repair.

Recent advances in genomics, such as RNA sequencing (RNA-Seq) have significantly contributed to the further understanding of cardiac development in humans. RNA-Seq has provided a comprehensive transcriptomic analysis of human heart development during early gestation [24]. Nebulin-related anchoring protein (NRAP) was among the genes that showed the largest fold change between 9- and 16-week gestational age. This protein is expressed at intercalated discs in cardiac muscle and is an actin-binding cytoskeletal protein [25, 26]. NRAP is involved during development in the myofibrillar assembly in the embryonic murine heart [27]. A patient with dilated cardiomyopathy with biventricular failure was found to have a homozygous truncating mutation (rs201084642) which introduced a stop codon to all NRAP isoforms [28]. Another study utilizing microarray RNA Seq analysis found that 316 genes were specifically associated with the human fetal heart, and 20 of those genes are the known candidates for congenital heart failure [29]. Specifically, the genes identified from the study associated with CHD include *PLN, NPPA, ANKRD1, MYH6, MYH7, ACTC1, CACNA1C, TBX20, HEY2, SLC8A1, RYR2, MYOCD, GJA1, ATP2A2, FBN2, SRPX, SCN5A, TBX5, HAND2,* and *KCNJ2*. This network of specific genes in the human fetal heart could represent a candidate common pathway close related to the development of CHD. An example of the

network is Notch-signaling cascade-related genes [30, 31]. Notch-signaling cascade plays a crucial role in cardiac cell fate regulation and orchestrates the morphogenesis of cardiac chambers and valves [32–34]. A recent study has suggested that *NOTCH1* haploinsufficiency alters specific gene networks affecting valve development and osteogenic factors, which in turn result in aortic valve disease [35]. *NOTCH1* ligands *JAG1* and *DLL4* have been shown to cause Alagille syndrome and aortic valve disease in human and animal models [36–38]. In addition, Genome-wide Copy Number Variant (CNV) analysis for congenital ventricular septal defects in the Chinese Han population revealed that VSD-related candidate genes are enriched in chromatin binding and transcription regulation, which are the biological processes underlying heart development. Specifically, this study suggested that *PAX3* and *LBX1* (in duplications) and *CRKL, GP1BB, PDLIM3, TBX1, TXNRD2* (in deletions) are associated with CHD. Enriched gene ontology (GO) revealed that these genes are involved in heart development, cardiovascular system development, and circulatory system development [39].

The extracellular matrix

The extracellular matrix (ECM) of the heart is important in translating the force generated from the shortening of sarcomere length to the cardiac chambers, resulting in stroke volume. The major components of the ECM are collagen types I and II, glycoproteins, and proteoglycans and the expression of these elements changes with development. The neonatal heart has a higher content of both total and type I collagen (which is stiffer and less compliant than type III collagen) when compared with the total protein content of the heart [40]. The collagen to total protein ratio reaches mature levels by about 5 months of life. This change, along with the greater water content of the immature myocardium, may partially explain the diminished diastolic function. Also, this relative lack of contractile elements reduces the ability of the neonatal myocardium to increase its inotropic state. A network of collagen-based connections, called the weave network, develops rapidly after birth, connecting myocytes and capillaries and allowing greater functional integrity to develop in response to the greater afterload stress on the heart [41]. This development of the ECM appears to be complete by approximately 6 months of age and results in a much more efficient transfer of force generated by sarcomere shortening to the cardiac chambers (Figure 9.4) [12].

The connection of the cardiac myocyte to the ECM is maintained by two specialized complexes that together comprise over 20 proteins. The costamere represents a major muscle multiprotein complex and produces a physical connection between the sarcomeres at the Z disk and the ECM. The integrin complex and the dystrophin-associated glycoprotein complexes are two major components of the costamere [42, 43] (Figure 9.5). The integrins are transmembrane glycoproteins consisting of two subunits, α and ß, which express several isoforms. Integrins such as integrin α5β1and α7β1 bind to collagen and fibronectin, which causes the attachment of the ECM to the myocytes, allowing force transduction to occur [44]. These integrins' expression is very dynamic; For example, the α5 subunit is prevalent in fetal and neonatal cardiomyocytes, while α7 replaces α5 at the onset of postnatal development [45]. However, subunit expression can switch and return to the fetal form under stress-producing myocyte hypertrophy and ischemia. Dystrophin-associated glycoprotein complexes also contribute to a substantial mechanical linkage from the ECM to the cardiac cytoskeleton, and contribute to force transduction [42, 43]. The proteins dystrophin, sarcoglycans, dystroglycan, and dystrobrevins are included in these complexes. These complexes play an integral role in cardiac function, and mutations in these proteins can be associated with cardiomyopathies, especially muscular dystrophy-associated cardiomyopathies. Reduction of dystrophin activity results in dilatation of all four cardiac chambers and reduced ventricular function. Mutations in dystrobrevins have been associated with left ventricular non-compaction.



Figure 9.4 Longitudinal sections through an adult rabbit cardiac myocyte (A) and a 3-week-old rabbit cardiac myocyte (B). Note the differences between myofibril organization and structure, as well as cell size. (Source: Nassar et al. [12]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Cell-to-cell connectivity

The intercalated discs mediate the cell-to-cell interactions that coordinate cardiac myocyte activity resulting in synchronous contraction, and maintaining the structural

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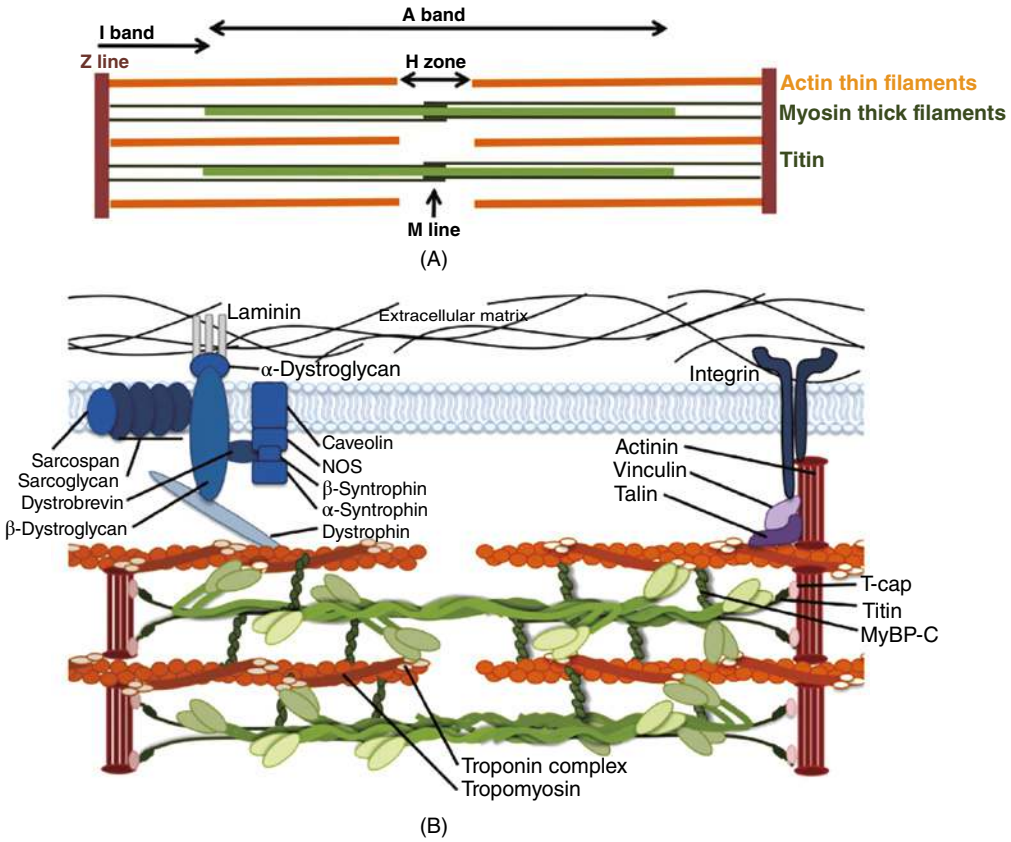


Figure 9.5 Anatomy of the cardiac sarcomere. (A) The basic organization of the sarcomere. The sarcomere forms the basic contractile unit. Thin filaments composed of actin are anchored at the Z line and form transient sliding interactions with thick filaments composed of myosin molecules. The M line, I band, and A band are anatomical features defined by their components (actin, myosin, and cytoskeletal proteins) and appearance in polarized light. Titin connects the Z line with the M line and contributes to the elastic properties and force production of the sarcomere through its extensible region in the I band. Coordinated shortening of the sarcomere creates contraction of the cardiomyocyte. (B) Major proteins of the sarcomere. Attachment to the extracellular matrix is mediated by costameres composed of the dystroglycan–glycoprotein complex and the integrin complex. Force transduction and intracellular signaling are coordinated through the costamere. The unique roles of each of these proteins are critical to the appropriate function of the heart. T-cap, titin cap; MyBP-C, myosin-binding protein C; NOS, nitric oxide synthase. (Source: Harvey and Leinwand [43]. Reproduced with permission of Rockefeller University Press.)

integrity of cardiac tissue [46] (Figure 9.6). These discs are situated in between cardiac myocytes at the longitudinal ends of the cells and consist of three types of connections: desmosomes, fascia adherens junctions, and gap junctions. The desmosomes have both intracellular and intercellular components. These structures serve to integrate signals from both cell-to-matrix and cell-to-cell interactions, ensuring force transmission, cell membrane integrity, and biochemical signaling. The fascia adherens junctions are responsible for holding the cardiac myocytes tightly together, and they anchor myofibrils and ensure transmission of contractile forces from cell to cell. Finally, the gap junctions form the electrical coupling apparatus between individual myocytes, ensuring rapid propagation of the electrical impulse, forming an electrical syncytium, and thus triggering the coordinated contraction of cardiac myocytes. Mutations in intercalated disc proteins have recently been found to be associated with cardiac disorders. These include adherens junctions mutations associated with heart failure and dilated cardiomyopathy, and desmosome complex mutations associated with some forms of arrhythmogenic right ventricular cardiomyopathy.

The preceding short review is meant to give the reader an idea of some of the aspects of the cellular biology of the developing circulation. The explosion of new information in this area, especially new data from human tissue, will lead to a more thorough understanding of the pathophysiology of disease states and will suggest avenues for future treatment. For a more complete treatment of this area, the reader is referred to several excellent reviews [47–49].

Innervation of the heart

Clinical observations in newborn infants have led to the hypothesis that the sympathetic innervation and control of the cardiovascular system are incomplete in the newborn infant compared with older children and adults and that the parasympathetic innervation is intact [5]. Examples of this include the frequency of bradycardia in the newborn in response to a number of stimuli, including vagal and vagotonic agents, and the relative lack of sensitivity in the newborn to sympathomimetic agents. Histologic studies in animal models have demonstrated incomplete sympathetic innervation in the neonatal heart when compared with the adult, but

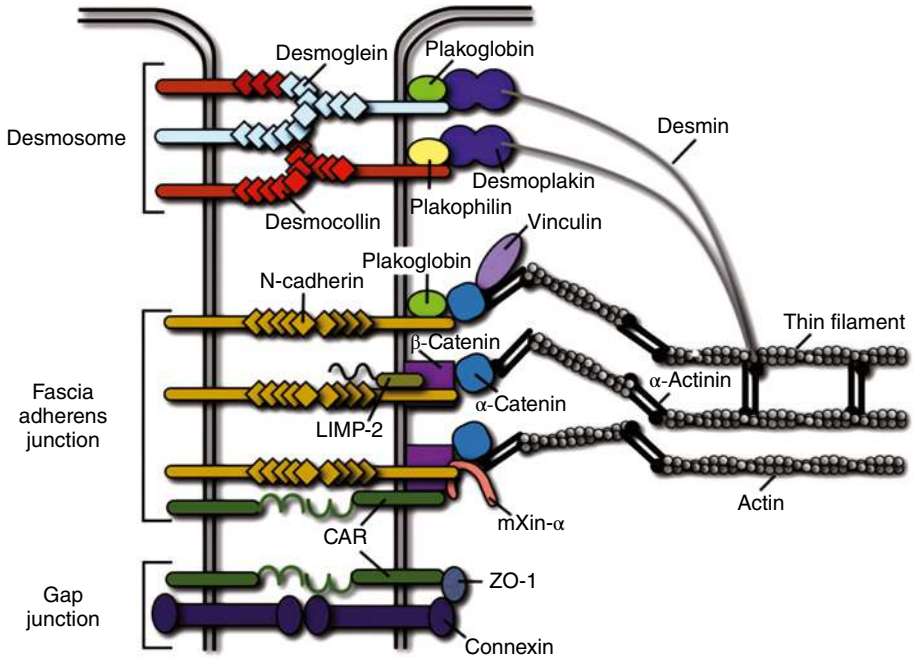


Figure 9.6 Major complexes and components of the cardiac intercalated disc. CAR, coxsackievirus and adenovirus receptor; LIMP-2, lysosomal integral membrane protein 2; mXinα, muscle-specific mouse Xinα; ZO-1, zona occludens 1. (Source: Sheikh et al. [46]. Reproduced with permission of Elsevier.)

no differences in the number or density of parasympathetic nerves [50, 51].

Autonomic cardiovascular control of cardiac activity can be evaluated by measuring heart rate variability in response to both respiration and beat-to-beat variability in systolic blood pressure [52]. The sympathetic and parasympathetic inputs into sinoatrial node activity contribute to heart rate variability changes, with greater heart rate variability resulting from greater parasympathetic input into sinoatrial node activity [53]. Studies using these methodologies for normal infants during sleep suggest that the parasympathetic predominance gradually diminishes until approximately 6 months of age, coinciding with greater sympathetic innervation of the heart similar to adult levels [54].

KEY POINTS: DEVELOPMENT FROM NEONATE TO OLDER INFANT AND CHILD

- The neonatal heart exhibits heart rate dependence, limited ability to increase contractile state, and limited tolerance for excessive afterload and preload.
- The costameres and dystrophin-associated glycoprotein complexes play central roles in connection of the cardiac myocyte to the ECM, thus forcing transduction in the heart.
- The intercalated discs maintain cell-to-cell connectivity between cardiac myocytes, allowing tight adhesion and electrical impulse transition to facilitate coordinated cardiac contraction.

Development from child to adult

Beyond the transition period from fetal to newborn life and into the first few months of postnatal life, there is not much human or animal information concerning the exact nature and extent of cardiac development at the cellular level. Most studies compare newborn or fetal animals with adult animals [55]. Cardiac chamber development is assumed to be influenced by blood flow [56]. Large flow or volume load in a ventricle result in ventricular enlargement. Small competent atrioventricular valves, as in tricuspid stenosis, result in lower blood flow and a small ventricle. Increases in myocardial mass with normal growth, as well as in ventricular outflow obstruction, are mainly due to hypertrophy of myocytes. Late gestational increases in blood cortisol are responsible for this growth pattern, and there is concern that antenatal glucocorticoids to induce lung maturity may inhibit cardiac myocyte proliferation. In the human infant, it is assumed that the cellular elements of the cardiac myocyte (i.e. adrenergic receptors, intracellular receptors and signaling, calcium cycling and regulation, and interaction of the contractile proteins) are similar to those in the adult by approximately 6 months of age. Similarly, cardiac depression by volatile anesthetic agents is greater in the newborn, changing to adult levels by approximately 6 months of age [57].

Normal values for physiologic variables by age

It is useful for the anesthesiologist to be aware of normal ranges for physiologic variables in premature and full-term newborns of all sizes and in infants and children of all ages (Table 9.1, Figure 9.7) [58]. Obviously, acceptable ranges for

Table 9.1 Normal heart rates and systolic blood pressure as a function of age

Age	Range of normal heart rates (beats/minute)	Range of normal systolic blood pressures, measured by oscillometric blood pressure device (mmHg)
Neonate (<30 days)	120–160	60–75
1–6 months	110–140	65–85
6–12 months	100–140	70–90
1–2 years	90–130	75–95
3–5 years	80–120	80–100
6–8 years	75–115	85–105
9–12 years	70–110	90–115
13–16 years	60–110	95–120
>16 years	60–100	100–125

Source: Blood pressure data are from references [40–43].

these variables are highly dependent on the individual patient's pathophysiology, but the wide range of "normal" values may reassure the practitioner to accept "low" blood pressure; for example, if other indices of cardiac function and tissue oxygen delivery are acceptable. Values for awake, healthy infants and children are often significantly different than in anesthetized patients and those with significant cardiac disease undergoing invasive procedures, especially with regard to the higher resting blood pressure values [59–61].

De Graaff and colleagues published an important study of over 116,000 ASA I and II patients from 10 centers undergoing non-cardiac procedures with mostly sevoflurane anesthesia and reported the range of blood pressure values in the preparation (pre-surgical) phase, and the surgical phase in patients from 0 to 18 years of age, measured by non-invasive oscillometric method (NIBP) [62] (Figure 9.8). The data were reported from electronic anesthesia medical records and were carefully refined to remove any artifacts. Age- and gender-specific reference curves were calculated which specified the systolic, diastolic, and mean blood pressures. The range at each age from +2 to −2 standard deviations (SD), representing 95% of all blood pressure values and thus constituting the range of "normal" blood pressures were included. For example, during the preparation phase before incision, the 50th percentile (0 SD) of mean arterial pressure ranged from 33 mmHg at birth to 66 mmHg at age 18 years in boys. The −2 SD (2.5th percentile) values for mean blood pressure ranged from 17 mmHg at birth to 47 mmHg at 18 years. The lowest reference ranges for anesthetized children are much lower (approximately 20 mmHg) than those for awake children; the 2.5th percentiles (−2 SD) of the systolic and mean non-invasive blood pressure (NIBP) of a 4-years-old boy are 85 and 60 mmHg, respectively, when non-anesthetized, and 68 and 38 mmHg, respectively, when anesthetized. The blood pressure values during the surgical phase were slightly higher in the youngest age groups less than 6 months, but very little different at older ages. This population of patients without CHD undergoing non-cardiac procedures with non-invasive blood pressure monitoring is clearly very different from cardiac surgery patients with invasive blood pressure monitoring but still can serve as an important reference point for the cardiovascular anesthesiologist.

Myocardial sequelae of longstanding CHD

Hypertrophy of the cardiac chambers is a common response to a number of different chronic pathophysiologic states. Wall thickness increases through hypertrophy of the cardiac myocytes and non-contractile elements. Hypertrophy reduces

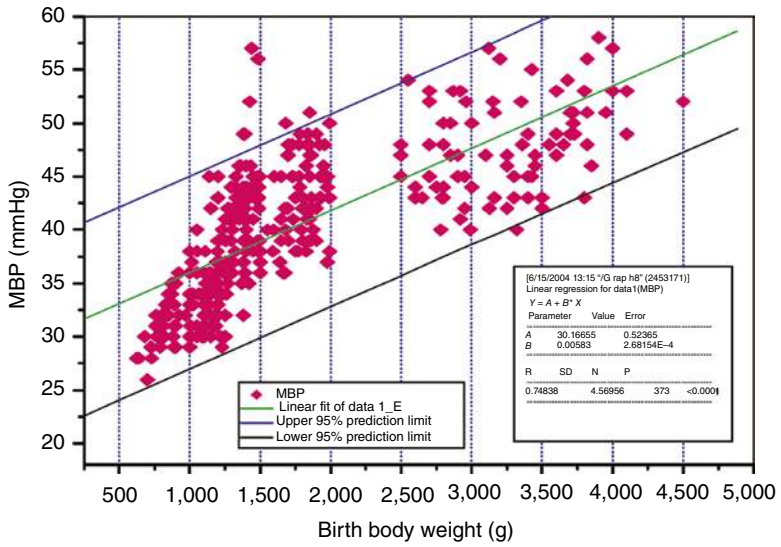


Figure 9.7 Linear regression of mean arterial pressure in 1-day-old neonates free of cardiopulmonary disease, measured by oscillometric methods in the awake state – 292 were premature and 81 full-term neonates. The middle green line is the 50th percentile, the upper blue line is the 95th percentile, and the lower black line is the 5th percentile. Note that in the 3.0 kg full-term neonate, normal mean arterial pressure can range from 37 to 56 mmHg. (Source: Pejovic et al. [58]. Reproduced with permission of Springer Nature.).

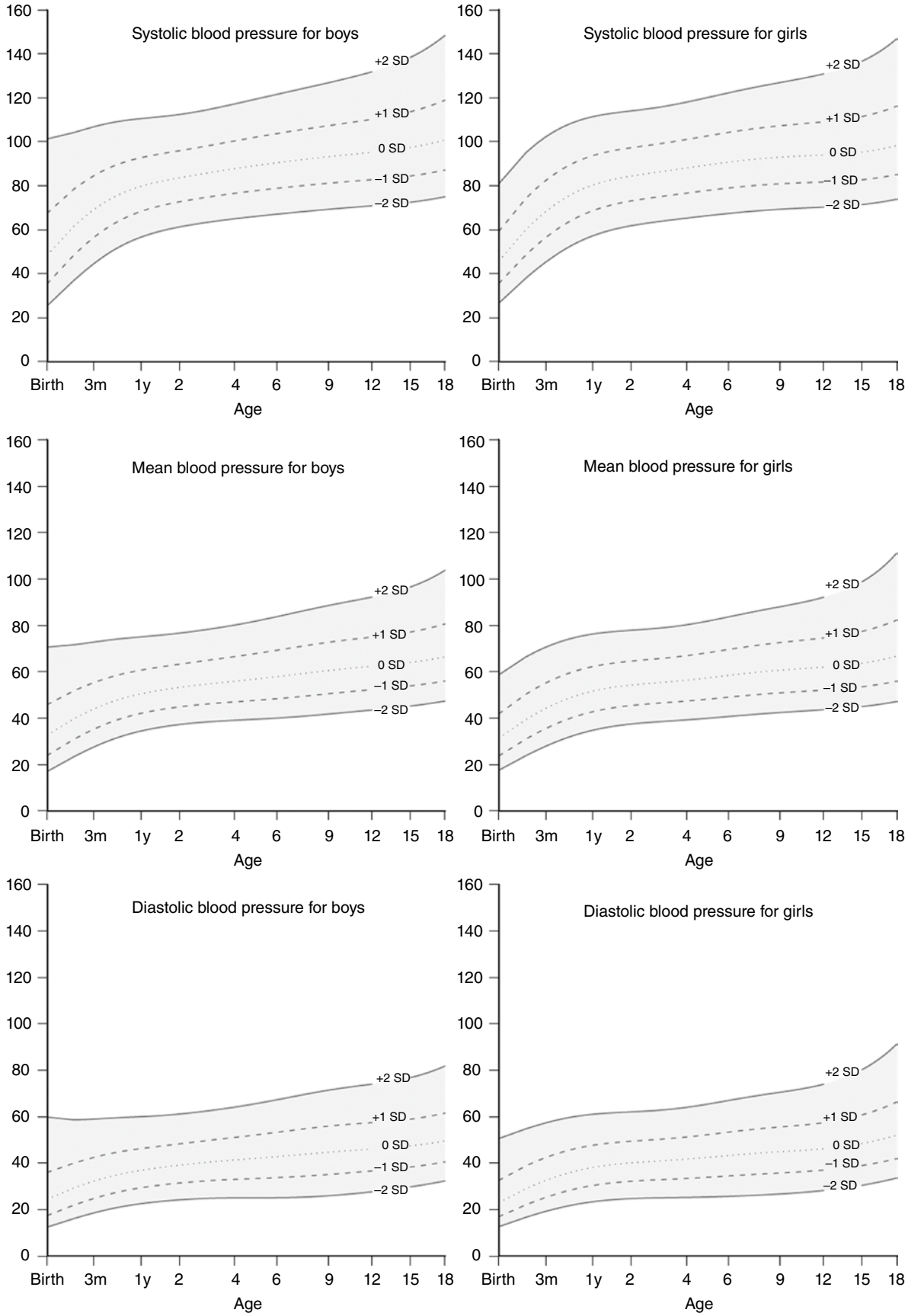


Figure 9.8 Reference curves for non-invasive blood pressure for boys and girls during anesthesia during the preparation phase before surgical incision, in relation to age. (Source: de Graaff et al. [62]. Reproduced with permission of Wolters Kluwer Health, Inc.)

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wall stress in the dilated heart but also serves to reduce ventricular function, particularly diastolic function. This reduction in function serves to reduce myocardial oxygen consumption in response to a wide variety of chronic stresses, in both pressure and volume overloaded ventricles [63].

Pressure overload hypertrophy results in altered gene expression in the cardiomyocyte. Myosin isoform expression (see later) changes from the faster-reacting α-myosin to the slower ß-myosin, reducing myocardial function [64]. Integrin-linked kinase expression is increased in patients with hypertrophic cardiomyopathy and induces hypertrophy in an animal model [65]. Altered expression or mutations of other genes that regulate the production of cardiac cytoskeletal proteins, such as dystrophin, occur in patients with end-stage cardiomyopathy [66, 67].

Cardiomyocyte receptor function in normal and diseased hearts

The adrenergic receptor

The adrenergic receptors (ARs) are a part of a large superfamily of receptors that mediate their biological responses through the coupling of a specific guanine nucleotide regulatory protein, or G protein [68]. This superfamily of receptors shares a common structural motif, characterized by seven hydrophobic domains spanning the lipid bilayer. The seven domains are attached by three internal loops and three external loops between the amine terminus and the cytoplasmic carboxy terminus. The function of this receptor family is dependent on a specific agonist (or ligand) binding to the receptor, which causes a conformational change in the receptor. This structural change permits the interaction between the intracellular portion of the receptor and the G protein. This interaction, also referred to as "coupling," inevitably links the activated receptor to a specific biological response. The regulation of the biological response is initiated by the specificity of the receptor for a particular extracellular agonist and the coupling of a specific G protein to that activated receptor.

Once an extracellular ligand (or agonist) is specifically recognized by a cell surface receptor, the receptor goes through a conformational change that exposes a specific region of the receptor complex to the intracellular side of the plasma membrane [69] (Figure 9.9). This conformation change triggers the interaction of the G protein with the amino acids of the third intracellular loop of the receptor and hence leads to G protein activation. There are three different G proteins: stimulatory G protein (G_s), inhibitory G protein (G_i), and the G_q protein. Under normal conditions, all of the ß receptors interact with the G_s, the α1 interacts with G_q, and the α2 interacts with G_i. Each G protein is a heterotrimer made up of three subunits: α, ß, and γ. The activation of the G-protein-coupled receptor causes an exchange of bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP) within the α subunit and initiates the disassociation of the ßγ subunit from the α subunit. The GTP-activated α subunit modulates the activity of a specific effector enzyme within a specific signaling pathway by catalyzing the hydrolysis of GTP to GDP and inorganic phosphate. This causes the transference of a high-energy phosphate group to an enzyme

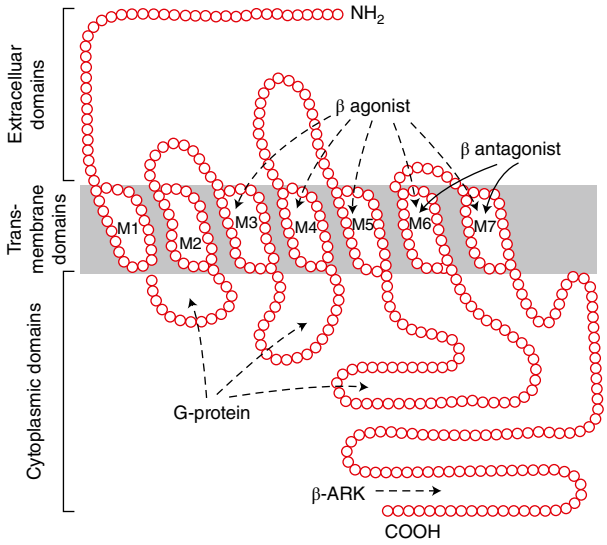


Figure 9.9 Molecular structure of the β-adrenergic receptor, demonstrating its three domains. The transmembrane domains serve as ligand-binding pockets for agonists (dashed arrows) and antagonists (solid arrows). The cytoplasmic domains interact with G proteins and β-adrenergic receptor kinases. (Source: Moss and Renz [68]. Reproduced with permission of Elsevier.)

and, in turn, causes the deactivation of the α subunit. This process will eventually lead to the reassociation of the α subunit with the ßγ complex. This cycle is continuously repeated until the agonist becomes unbound from the receptor. Downstream of enzyme activation, the production of a second messenger regulates the biological response.

Adrenergic receptors have been subdivided into two groups of receptors based on the results of binding studies using a series of selective agonists and antagonists. In 1948 Ahlquist used the difference in rank orders of the potency of a series of agonists to separate the ARs into two principal receptor groups, the α and ß receptor groups [70]. These findings have been confirmed repeatedly with the development of drugs that function to selectively antagonize the α receptor with no effect on the ß receptor. Soon after the distinction between the α and ß receptor types was known, it became more evident that the separation of α and ß receptors was not sufficient to explain pharmacological studies using rank order of potency for an antagonist, differing from an agonist because it blocks the biological response. With the advent of radioligand-labeled antagonists and new molecular cloning techniques examining receptor gene expression, it became clear that the two principal receptor groups could be further subdivided into additional subtypes.

To date, within the ß-adrenergic group, four different subtypes have been identified: $ß_1$, $ß_2$, $ß_3$, and $ß_4$. Pharmacologically, $ß_1$ and $ß_2$ are differentiated by their affinities to different catecholamines: epinephrine, norepinephrine, and isoproterenol. $ß_1$ has a similar affinity to epinephrine and norepinephrine, while $ß_2$ has a higher affinity to epinephrine than to norepinephrine. Both $ß_1$ and $ß_2$ have the same affinity to isoproterenol. The $ß_3$ and $ß_4$ receptors have minor roles in cardiovascular function and will not be discussed further.

The expression and distribution of each subtype are highly dependent on the organ, which adds another level of

specificity. The distribution of a particular receptor in two different tissue types may result in two different functions. When examining the cardiovascular response to adrenergic stimulation, the ß$_1$ receptor is predominantly expressed in heart tissue. The stimulation of the receptor subtype leads to both inotropic and chronotropic effects on cardiac function, resulting in an increase in the myocardial contractile force and a shortening of contractile timing, respectively. While ß$_2$ can also be found in the heart, it is mostly expressed in vascular smooth muscle tissue. The distribution and function relevance of this receptor subtype in the heart are controversial and may change with alterations in cardiac function. The percentage of ß$_2$ receptors in the non-failing heart averages about 20% in the ventricle [71] and 30% in the atrium. The ratio of ß$_1$ to ß$_2$ receptors is approximately 75 : 25% in the ventricles of younger hearts [72, 73].

Each signaling pathway is specific to each adrenergic receptor. Once the agonist binds to the ß$_1$ receptor causing the coupling of the G protein, the G-protein α subunit becomes activated followed by an increase in adenylate cyclase activity, which induces the conversion of ATP to cAMP. The second messenger, cAMP, phosphorylates protein kinase A (PKA). The function of a kinase is to phosphorylate other target proteins, which initiates a biological response. PKA phosphorylates many intracellular targets, including calcium channels, troponin I, and ryanodine receptors. PKA also plays a central role in regulating calcium sensitivity [74].

The ß$_2$ receptor has also been shown to function through the cAMP signaling pathway, causing the activation of PKA, but not nearly to the extent of ß$_1$ in cardiomyocytes [74]. The response of this stimulation appears to have a larger effect on smooth muscle; for example, the vascular smooth muscle. In this tissue type, the stimulation of ß$_2$ and the subsequent increase in cAMP promote the vasodilation of vascular smooth muscle and may lead to alterations in blood pressure. In these tissues, the effect of ß$_1$ stimulation appears to be minimal, due to the lack of ß$_1$ receptors in the smooth muscle.

Similar to the ß receptors, the α receptors can be pharmacologically subdivided into α_1 and α_2. The α receptor is distributed in most vascular smooth muscle and, to a lesser extent, in the heart. The α_2 receptor has been found in some vascular smooth muscle; however, its major functional importance is as a presynaptic receptor in the central and peripheral nervous systems. The use of molecular techniques has identified three additional subtypes of the α_1 receptor (α_{1A}, α_{1B}, and α_{1D}) and three additional subtypes of the α_2 receptor [68]. Binding of an agonist to an α_1 receptor in the heart or vascular smooth muscle results in activation of the G_q subunit of the G protein, which activates phospholipase C (see later), producing diacylglycerol and inositol-1,4,5-triphosphate, which releases Ca^{2+} from the sarcoplasmic reticulum and increases vascular smooth muscle tone or cardiac contractility. A schematic classification of adrenergic receptors incorporating recent knowledge of molecular pharmacology and signal transduction is presented in Figure 9.10 [68].

The adrenergic receptor concentration in cardiac tissue is very small and measured as fentomoles/mg protein. However, the response to stimulation of the receptor is significantly amplified by the signal that occurs downstream of the receptor. In rat ventricular myocytes, the ratio between the ß receptors and the next two downstream signaling components (ß receptor : G protein : adenylate cyclase) is 1 : 200 : 3 [76]. This demonstrates how a large response can be initiated by the activation of a small number of receptors. In addition, it also shows that the rate-limiting component that ultimately regulates intracellular production of cAMP is receptor density and the enzyme concentration of adenylate cyclase.

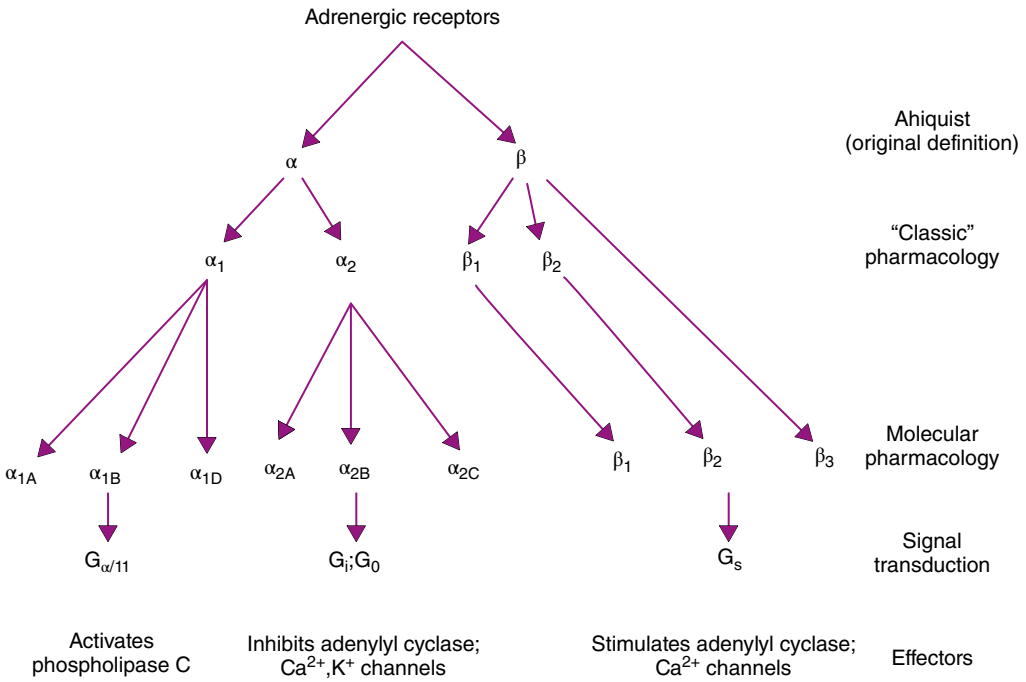


Figure 9.10 A schematic classification of adrenergic receptors. (Source: Moss and Renz [68]. Reproduced with permission of Elsevier.)

Developmental changes in adrenergic receptor signaling

Information concerning changes in adrenergic receptor function during the transition from neonatal to more mature myocardial development is limited to a few animal studies. As noted above, the neonatal heart has a limited inotropic response to catecholamine administration.

ß-Adrenergic receptor density is higher in the ventricular myocardium of neonatal versus adult rabbits, but the inotropic response to the same concentration of isoproterenol is significantly greater in adult tissue [77]. In the neonatal rat, the mechanism of the ß-adrenergic-mediated increase in contractility is entirely due to $ß_2$ stimulation, whereas in the adult rat it is due solely to $ß_1$ receptor activation. Coupling of the $ß_2$ receptor to G_i protein action is apparently defective in the neonatal rat because the ratio of G_i to G_s subunits is much higher in the neonate. The relative proportion of $ß_1$ and $ß_2$ receptors is the same in neonatal and adult hearts (83% $ß_1$, 17% $ß_2$) and approximates the ratio measured in children with simple acyanotic CHD, which is about 78% $ß_1$: 22% $ß_2$ [72].

There is animal and human evidence that α-adrenergic receptor-mediated chronotropic and inotropic effects on the cardiac myocyte change with development. In the neonatal animal model, α-stimulation produces positive inotropic and chronotropic effects, whereas in the adult it produces negative effects [78, 79]. The chronotropic response to α_1 stimulation diminished with increasing age in children being evaluated for autonomic dysfunction after vagal and sympathetic blockade [80].

Calcium cycling in the normal heart

Calcium assumes a central role in the process of myocardial contraction and relaxation, serving as the second messenger between depolarization of the cardiac myocyte and its contraction mediated by the actin-myosin system. Calcium's role in this excitation-contraction coupling in the normal mature heart will be reviewed briefly before discussion of developmental changes and changes with heart failure [81].

Cardiac muscle cell contraction depends on an increase in intracellular Ca^{2+} above a certain threshold, and relaxation ensues when intracellular Ca^{2+} falls below this threshold. Two major regions of Ca^{2+} flux occur: across the sarcolemmal membrane (slow response) and release from internal stores, the sarcoplasmic reticulum (rapid release and reuptake) [82, 83] (Figure 9.11). The primary site of entry of Ca^{2+}

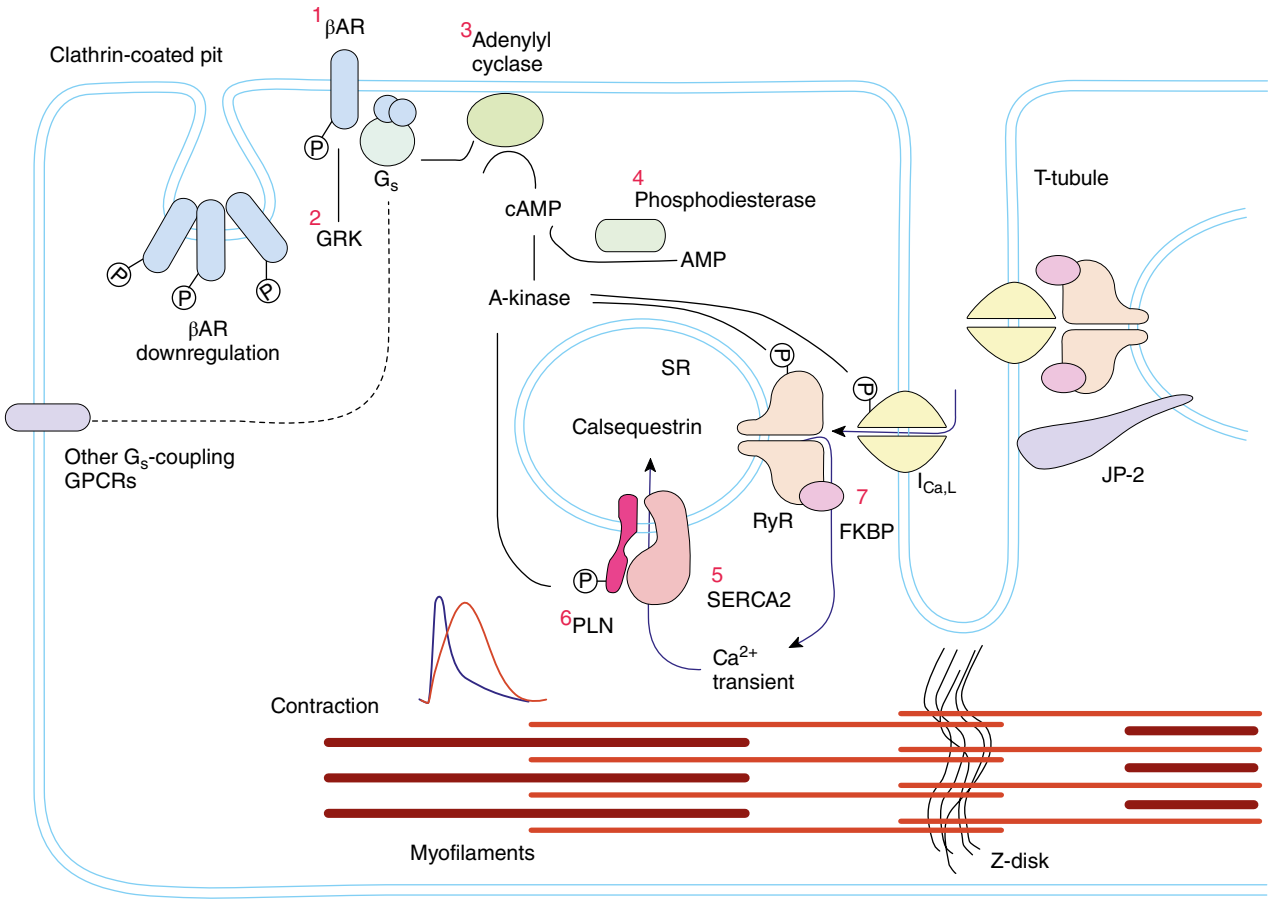


Figure 9.11 Calcium cycling and its relationship to the β-adrenergic receptor system and myocyte myofilaments. See text for discussion. A-kinase, protein kinase A; βAR, β-adrenergic receptor; cAMP, cyclic AMP; FKBP, FK-506 binding protein; G_s, stimulatory G protein; GPCR, G-protein coupling receptor; GRK, G-receptor kinase; $I_{ca,L}$, L-type Ca^{2+} channel; JP-2, junctophilin-2; PLN, phospholamban; RyR, ryanodine receptor; SERCA2, sarcoplasmic reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum. Encircled P represents sites of phosphorylation by the various kinases. Numbers 1 through 7 represent targets for pharmacologic therapy in cardiac failure. (Source: Hoshijima and Chien [83]. Reproduced with permission of American Society for Clinical Investigation.)

through the sarcolemmal membrane is through the L-type, or low-voltage-dependent Ca^{2+} channels, which occurs in two types, a low-threshold, rapidly inactivating channel, and a higher threshold, more slowly inactivating channel [84]. Depolarization of the sarcolemmal membrane triggers the opening of these channels, resulting in the release of a large amount of Ca^{2+} from the sarcoplasmic reticulum (SR), the major internal Ca^{2+} storage organelle. Ca^{2+} entry through the slowly inactivating channels serves to fill the SR with adequate Ca^{2+} stores. Removal of Ca^{2+} from the cytoplasm to the exterior of the cell occurs via two major mechanisms: the sodium-calcium (Na^{+}—Ca^{2+}) exchanger, and the calcium ATPase pump. The Na^{+}—Ca^{2+} exchanger usually serves to exchange three sodium ions (moving into the cell) for one Ca^{2+} (moving out of the cell), although the reverse action, as well as a 1:1 exchange, are possible [85]. The Ca^{2+}-ATPase pump actively transports Ca^{2+} (in a 1:1 Ca^{2+}/ATP ratio) out of the cell in an energy-dependent, high-affinity but low-capacity manner [86]. The affinity of the sarcolemmal Ca^{2+}-ATPase pump is enhanced by calmodulin, a binder of free cytoplasmic Ca^{2+}. Although the calcium movement through the sarcolemma plays an important role in balancing internal and external Ca^{2+} concentrations and in supplying Ca^{2+} to replenish SR Ca^{2+} stores, and in initiating the Ca^{2+}-induced release of Ca^{2+} from the SR, it is important to recognize that the amount of Ca^{2+} flux is far less than across the SR, the far more important mechanism for excitation-contraction coupling in the mature heart [87]. The sarcolemmal Ca^{2+} flux mechanisms play a much more important role in the excitation-contraction coupling of the neonatal (immature) heart.

The massive release and reuptake of Ca^{2+} responsible for activation and deactivation of the actin-myosin complex and cardiomyocyte contraction and relaxation occur at the level of the SR. The SR is a closed, intracellular membranous network that is intimately related to the myofilaments responsible for contraction [88, 89] (Figure 9.12). The SR is connected to the sarcolemmal membrane via the transverse tubule (T-tubule) system. Depolarization of the sarcolemmal membrane results in the transfer of charge down the T-tubules to the SR, resulting in the opening of SR Ca^{2+} channels and the release of large amounts of Ca^{2+} into the cytoplasm, where

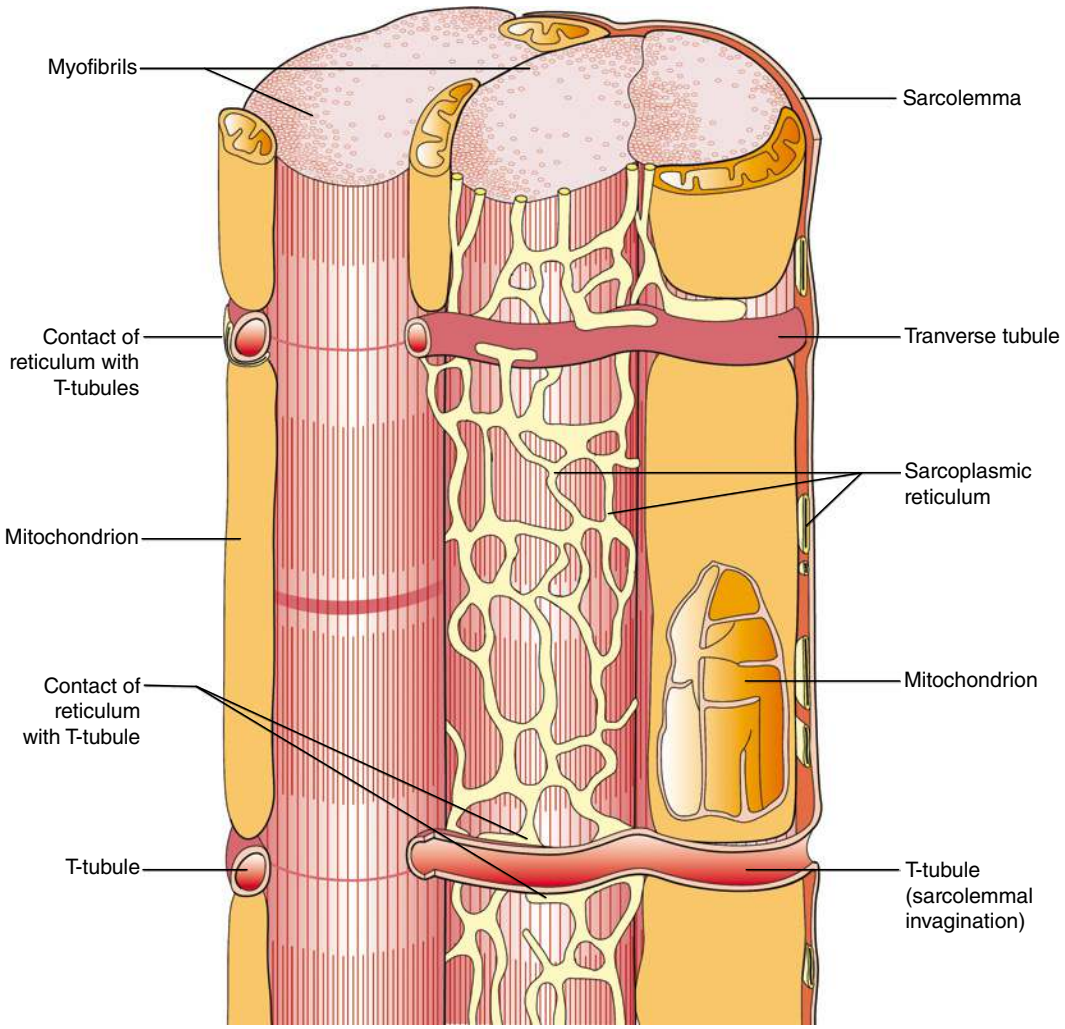


Figure 9.12 Normal, mature cardiac myocyte structure. (Source: Bloom and Fawcett [89]. Reproduced with permission of Elsevier.)

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it can then bind to troponin and initiate the actin-myosin interaction. The SR is divided into longitudinal SR and terminal cisternae; the latter connects to the T-tubules. The terminal cisternae are primarily involved in the release of Ca^{2+}, and the longitudinal SR in its reuptake [90].

The primary Ca^{2+} release mechanism of the SR is the ligand-gated Ca^{2+}-release channels (also known as the ryanodine receptors) that bind to the drug ryanodine. The channels are activated by two primary mechanisms: depolarization via the T-tubules, and binding of intracellular Ca^{2+} itself. The predominance of one mechanism over the other differs in cardiac vs. skeletal muscle. The proximity of the L-type sarcolemmal Ca^{2+} channels in the T-tubules to the ligand-gated Ca^{2+}-release channels allows the depolarization to rapidly allow Ca^{2+} into the cell and open the SR Ca^{2+} channels. These ligand-gated Ca^{2+} release channels close when the cytosolic Ca^{2+} concentration increases; normally it opens at 0.6 µM Ca^{2+} and closes at 3.0 µM Ca^{2+}.

The reuptake and sequestration of Ca^{2+} lead to the relaxation of the cardiac myocyte and is an active transport mechanism, primarily involving hydrolysis of ATP by the SR Ca^{2+}-ATPase (SERCA), located in the longitudinal SR [91]. It binds two Ca^{2+} ions with high affinity and rapidly transports them to the inside of the SR. This transport system differs from the sarcolemmal membrane: it has a higher affinity, allows for more rapid transport, and is not sensitive to calmodulin. Ca^{2+} is stored in the SR by calsequestrin, a high-capacity, low-affinity protein that acts as a Ca^{2+} sink.

There are two other proteins with essential roles in the regulation of Ca^{2+} flux: phospholamban and calmodulin [92, 93]. Phospholamban is associated with the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and can be phosphorylated by at least four different protein kinases (see earlier): cAMP-dependent, Ca^{2+}/calmodulin-dependent, cyclic guanosine monophosphate (cGMP)-dependent, or PKC. When phosphorylated, phospholamban increases the affinity of the SERCA for Ca^{2+}, facilitating Ca^{2+} flux back into the SR, thus affecting the inotropic and lusitropic state of the heart. Phospholamban plays an important role in the ß-adrenergic-mediated increase in the inotropic state of the heart. Calmodulin is a Ca^{2+} storage protein with four binding sites, found in the cytoplasm, which interacts with the sarcolemmal Ca^{2+}-ATPase (increasing its affinity for Ca^{2+}), the SR ligand-gated Ca^{2+}-release channel (inhibits its activity at optimal cytoplasmic Ca^{2+}), and binds to the Ca^{2+}/calmodulin-dependent protein kinase [93]. Mutations in the phospholamban gene have been described and may be a rare cause of dilated cardiomyopathy [94].

The increase in intracellular cytoplasmic Ca^{2+} initiates the contractile process. Myosin is the major component of the thick filaments, which make up the microscopic structure of the myofibril, and its interaction with actin (the major component of the thin filaments) provides the mechanical basis of cardiac muscle cell contraction [95]. Actin and myosin make up approximately 80% of the contractile apparatus and are arranged in a parallel, longitudinal fashion, projecting from a Z-line or band (Figure 9.13) to form the basic contractile unit called the sarcomere [96]. A three-dimensional lattice consisting of interdigitated thick and thin filaments in a hexagonal array, with three thin filaments in close proximity to each thick filament, is formed. The actin and myosin are linked by projections on the myosin protein called S1 cross-bridges, which bind to actin, and, via an energy-dependent hinge-like mechanism, produce the sliding filament cross-bridge action that is thought to produce sarcomere shortening and lengthening. The lattice is held together by connecting proteins such as titin, nebulin, and α-actinin [97]. The actin-myosin interaction is initiated when Ca^{2+} binds to troponin, a protein closely connected to actin, which consists of three subunits: a Ca^{2+}-

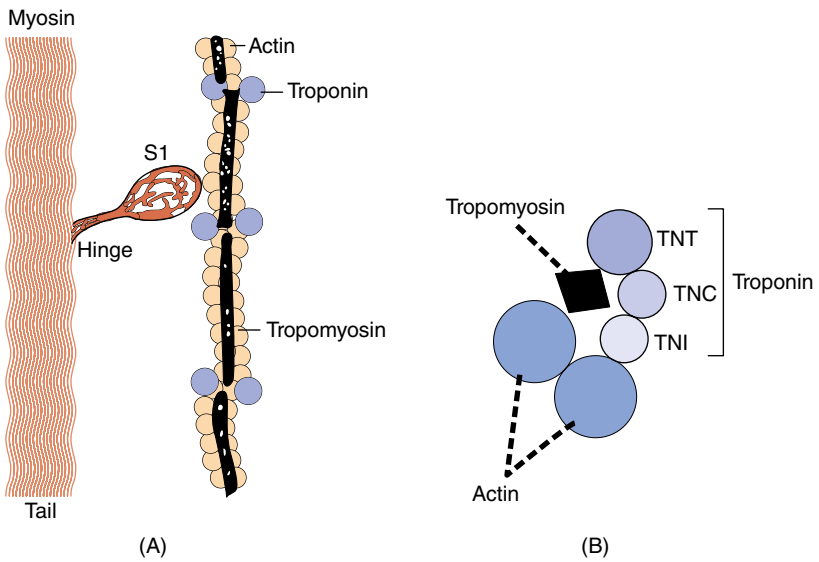


Figure 9.13 (A) Single thick and thin filament showing the S1 cross-bridge and hinge mechanism. (B) Relationship of actin to tropomyosin and the three troponin subunits. See text for explanation. TNC, a Ca^{2+}-binding subunit; TNI, inhibitory subunit; TNT, tropomyosin-binding unit. (Source: Michael [96]. Reproduced with permission of Wolters Kluwer.)

Table 9.2 Summary of major differences between neonatal and mature hearts

	Neonatal	Mature
Physiology		
Contractility	Limited	Normal
Heart rate dependence	High	Low
Contractile reserve	Low	High
Afterload tolerance	Low	Higher
Preload tolerance	Limited	Better
Ventricular interdependence	Significant	Less
Ca^{2+} cycling		
Predominant site of Ca^{2+} flux	Sarcolemma	SR
Dependence on normal Ca^{2+}	High	Lower
Circulating catecholamines	High	Lower
Adrenergic receptors	Down-regulated, insensitive	Normal
	β_2, α_1 predominant	β_1 predominant
Innervation	Parasympathetic predominates; sympathetic incomplete	Complete
Cytoskeleton	High collagen and water content	Lower collagen and water content
Cellular elements	Incomplete SR, disorganized myofibrils	Mature SR, organized myofibrils

SR, sarcoplasmic reticulum.

binding subunit (TNC), a tropomyosin-binding unit (TNT), and an inhibitory subunit (TNI). TNC can bind up to four Ca^{2+} ions, and this produces a conformational change on the thin filament, which allows the S1 myosin head cross-bridges to attach [98]. This also changes the TNI subunit's conformation and allows tropomyosin, another protein integral in filament interaction, to move aside and expose the binding sites on actin, allowing the strong binding to the S1 cross-bridges. With Ca^{2+} present, actin causes myosin ATPase to hydrolyze one ATP molecule, providing energy that results in the S1 myosin head pulling on the thin filament, resulting in sarcomere shortening. Troponin C is the most important aspect of the regulation of cardiocyte contraction and has a steep response curve to local levels of Ca^{2+}. The reuptake of Ca^{2+} into the SR causes Ca^{2+} levels to rapidly decline, and the inhibitory form of the troponin, tropomyosin, actin complex returns, resulting in the reversal of the cross-bridge binding and thus sarcomere relaxation.

Besides calcium, many other regulatory mechanisms exist to influence the interaction and sensitivity of Ca^{2+} binding to troponin. These mechanisms include ß-adrenergic stimulation, thyroid hormone, and phosphorylation by cAMP-dependent protein kinases.

Developmental changes in calcium cycling

Several aspects of the excitation-contraction system are different in the immature heart. The T-tubule is not fully formed [99], and the SR has less storage capacity and less structural organization [100], less mRNA expression [101, 102], and less responsiveness to chemical blockade [103, 104]. The TNI changes from a predominately cAMP-insensitive form to a cAMP-responsive form by 9 months of age, an additional factor contributing to the increased responsiveness seen with ß-adrenergic stimulation after the neonatal period [104]. All of this information has led to the theory that the neonatal cardiac myocyte is more dependent than the mature heart on free cytosolic Ca^{2+} fluxes, and more susceptible to blockade of the L-type Ca^{2+} sarcolemmal channels as a mechanism of myocardial depression. The latter is thought to be the mechanism producing greater myocardial depression observed with halothane in neonatal rat models compared with sevoflurane, and the same phenomenon is seen clinically [105]. A summary of the major differences in cardiac development and function between the neonatal and mature heart is presented in Table 9.2.

Thyroid hormone

Tri-iodothyronine (T3) has a critical role both in the development of the cardiovascular system and in acute regulation and performance. Normal T3 levels are essential for normal maturation and development of the heart through the expression of genes responsible for the production of the cardiac contractile proteins, elements of the calcium cycling apparatus, and development and density of ß-adrenergic receptors [106]. There are cell nucleus-mediated effects from exogenous T3 that occur from an increase in protein synthesis and require at least 8 hours to develop. These include upregulation of ß-adrenergic receptors, an increase in cardiac contractile protein synthesis, an increase in mitochondrial density, volume, and respiration, an increase in SERCA mRNA, and changes in MHC isoforms. However, there are acute effects of T3 on cardiac myocytes that occur in minutes from interactions with specific sarcolemmal receptors and include stimulation of L-type Ca^{2+}-pump activity, stimulation of SR Ca^{2+}-ATPase activity, increased protein kinase activity, and decrease in phospholamban [107]. Cardiac surgery and cardiopulmonary bypass interfere with the conversion of thyroxine (T4) to T3, and serum levels decrease significantly after cardiac surgery in infants and children [108]. T3 infusions improve myocardial function in children after cardiac surgery and reduce intensive care unit stay [109].

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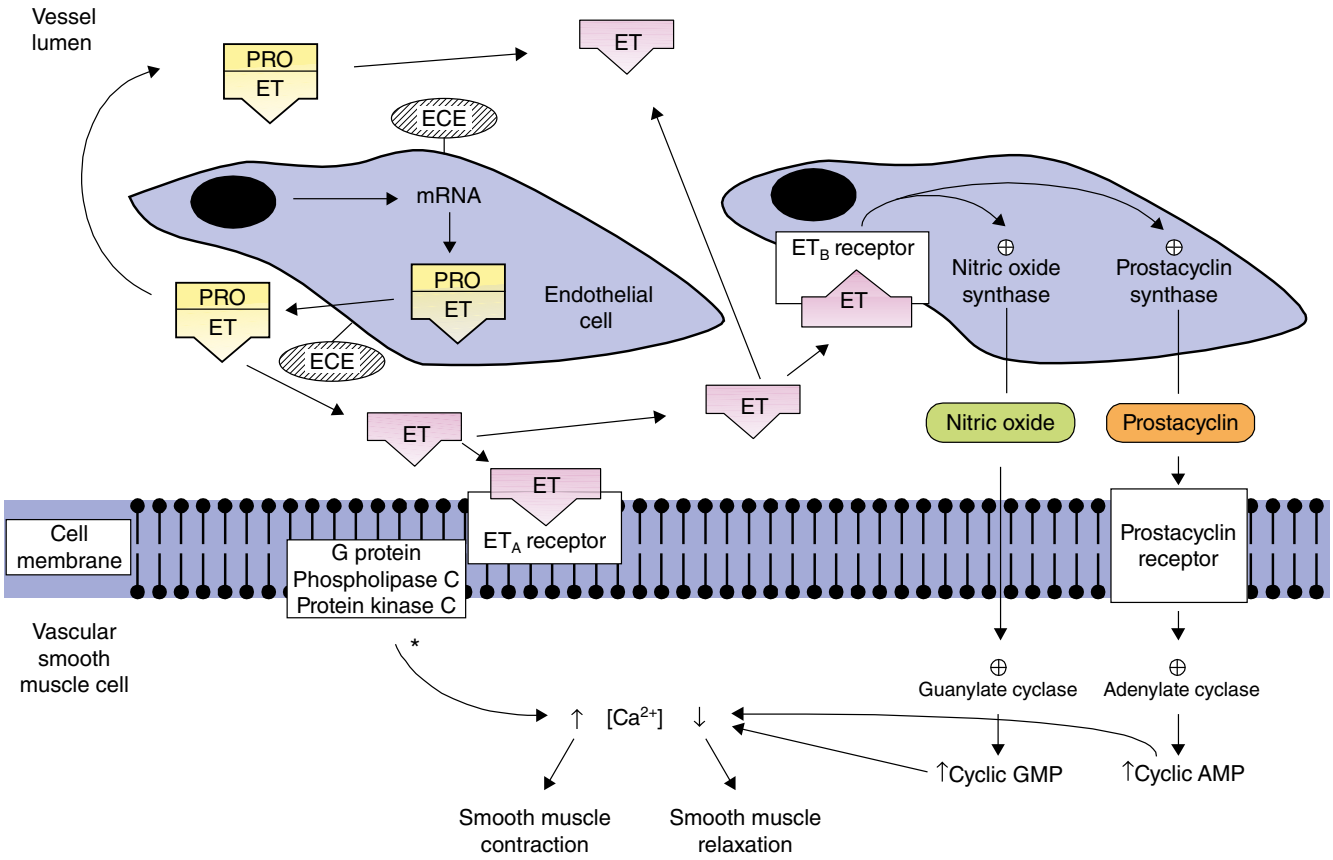


Figure 9.14 Schematic of some major mediators of vascular tone in the pulmonary circulation. ECE, endothelin-converting enzyme; ET, endothelin-1; PROET, proendothelin-1. See text for explanation. (Source: Haynes and Webb [110]. Reproduced with permission of The Biochemical Society and the Medical Research Society.)

KEY POINTS: CARDIOMYOCYTE RECEPTOR FUNCTION IN NORMAL AND DISEASED HEARTS

- The adrenergic receptor system, particularly the β-receptor system, plays a central role in regulating cardiac contractility through G protein and adenylate cyclase coupling.
- Calcium cycling in the neonatal heart is characterized as immature, with underdeveloped T-tubules and sarcoplasmic reticulum, not reaching a mature state until an estimated 6–12 months of age.
- Thyroid hormone is essential for normal gene expression for production of cardiac contractile proteins, calcium cycling apparatus, and adrenergic receptor density, as well as acute effects to increase the sensitivity of adrenergic receptors and efficiency of calcium cycling.

Regulation of vascular tone in systemic and pulmonary circulations

The regulation of vascular tone is an important consideration in the understanding and treatment of CHD. Both the systemic and pulmonary circulations have complex systems to maintain a delicate balance between vasodilating and vasoconstricting mediators in normal patients. Abnormal responses may develop that lead to pulmonary or systemic hypertension, or conversely vasodilation. A schematic representation of some of these mediators is shown in Figure 9.14 [110]. To some extent, the control mechanisms reviewed are present in both the systemic and pulmonary circulations; however, certain mechanisms are more important in one circulation. For example, the endothelial-mediated systems (nitric oxide–cGMP pathways and others) predominate in the pulmonary circulation (low-resistance circulation), whereas the phospholipase systems predominate in the systemic circulation (high-resistance circulation). The endothelium-dependent control of vascular tone plays a significant role in the transition from fetal to postnatal circulation, with pathologic persistence of fetal endothelial milieu contributing to the transitional circulation and pulmonary hypertension, both of which may influence the pathophysiology of CHD [111].

Pulmonary circulation

Metabolites of arachidonic acid, called eicosanoids, are produced from cells and a group of eicosanoids acts as vasoactive agents. Eicosanoids metabolized via the lipoxygenase pathway will form leukotrienes, and those metabolized via the cyclooxygenase pathway form the prostaglandins. Important

vasodilating prostaglandins include PGE_1, which also promotes and maintains patency of the ductus arteriosus. Prostacyclin, PGI_2, is a potent pulmonary vasodilator [112]. Prostaglandins act on the vascular smooth muscle of the systemic and pulmonary circulations by binding to receptors in the smooth muscle cell membrane, activating adenylate cyclase, and increasing cAMP concentrations, which lead to lower Ca^{2+} levels and a reduction of vascular tone. Thromboxane A_2 is a potent leukotriene that has the opposite effects of the prostaglandins, producing vasoconstriction and platelet aggregation. Imbalance in this system caused by chronic hypoxia can lead to chronic pulmonary hypertension [113, 114].

Nitric oxide (NO) is an endothelium-derived relaxant factor that causes relaxation of vascular smooth muscle cells after diffusing into the cell and activating guanylate cyclase, increasing the concentration of cGMP, leading to a reduction in the local concentration of Ca^{2+} and thus reducing vascular tone [115]. Calcium-sensitive potassium channels contribute to the vasodilatation caused by NO via a cGMP-dependent protein kinase [116]. NO is formed from L-arginine by NO synthase and is almost immediately inactivated by binding to hemoglobin. Phosphodiesterase V breaks down cGMP; hence, the phosphodiesterase-inhibiting drugs, such as sildenafil, potentiate NO-mediated vasodilation [117].

Endothelins are powerful endothelium-derived vasoactive peptides, and endothelin-1 (ET-1) is the best characterized one. ET-1 is produced from proendothelin-1 by endothelin-converting enzymes in the endothelial cells of the systemic and pulmonary vasculature. Increased pressure, shear stress, and hypoxia can lead to increased production of ET-1 in the pulmonary circulation. Two ET-1 receptors, ETA and ETB, mediate effects on smooth muscle vascular tone [118]. The ETA receptor is found on the smooth muscle cell membrane and mediates vasoconstriction, while the ETB receptor is located on the endothelial cell itself, and results in increased NO synthase activity, producing vasodilation. The primary activity of ET-1 appears to be to stimulate the ETA receptor and indeed increased levels of ET-1 are found in many pulmonary hypertensive states such as Eisenmenger syndrome and primary pulmonary hypertension [119]. ET-1 increases in response to shear stress, hypoxia, or ischemia, and results in elevated intracellular Ca^{2+} and increased sensitivity to Ca^{2+}, increasing pulmonary vascular tone and pressure [114].

Systemic circulation

There are multiple levels of control over the peripheral circulation. Neural control by the sympathetic and parasympathetic nervous systems is produced from the stimulation of receptors on the afferent limb such as stretch receptors within the walls of the heart, and baroreceptors in the walls of arteries, such as the aortic arch and carotid sinuses. Stretch in the arterial wall stimulates the baroreceptors, producing vasodilation and heart rate slowing mediated by the vasomotor centers of the medulla [120]. Atrial stretch receptors inhibit the secretion of vasopressin from the hypothalamus. The efferent limb of the autonomic nervous system consists of sympathetic and parasympathetic nerve fibers. The sympathetic nerves can be divided into vasoconstrictor and vasodilator fibers. When stimulated, the vasoconstrictor fibers release norepinephrine, activating α-adrenergic receptors and producing vasoconstriction. The vasodilator fibers release acetylcholine or epinephrine and are mainly present in skeletal muscle. Parasympathetic fibers are vital in the control of heart rate and function but have only a minor role in controlling peripheral circulation [121].

Hormonal control and receptor-mediated intracellular signaling are other important mechanisms. Norepinephrine primarily stimulates peripheral α receptors and causes vasoconstriction. It is secreted by the adrenal medulla and by sympathetic nerves in proximity to the systemic blood vessels. Epinephrine is also secreted by the adrenal medulla, but its primary action is to stimulate the $ß_2$ receptors in the peripheral circulation, causing vasodilation through cAMP-mediated reductions in intracellular Ca^{2+} concentrations.

Angiotensin II is produced by activation of the renin-angiotensin-aldosterone axis in response to reduced flow and pressure sensed by the juxtaglomerular apparatus in the kidney. Renin produces angiotensin I by cleaving angiotensinogen, and angiotensin II is produced when angiotensin I passes through the lung by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor, and also induces the hypothalamus to secrete vasopressin (antidiuretic hormone), which also has vasoconstrictor properties.

Atrial natriuretic factor (ANF) is released from atrial myocytes in response to stretch (elevation of right or left atrial pressure) on the atrium. ANF has vasodilatory and cardioinhibitory effects and causes sodium retention from decreased tubular reabsorption of sodium in the kidney [122]. B-type natriuretic peptide (BNP) is released by the ventricular myocardium, also in response to stretch, and causes an increase in cGMP, leading to vasodilatation in both arterial and venous systems. In addition, it increases urinary sodium and water excretion [123].

Second messenger systems affect the activation of receptors on systemic vascular cell membranes, leading to changes in vascular tone. The phosphoinositide signaling system is the common pathway for many of these agonists [120] (Figure 9.15). Membrane kinases phosphorylate phosphatidylinositol, which is an inositol lipid located mainly in the inner lamella of the plasma membrane, producing phosphatidylinositol 4,5 biphosphate. The second messenger, inositol 1,4,5-triphosphate, is produced from this compound by the action of the enzyme phospholipase C (PLC) [124]. The sequence begins with the binding of an agonist, such as angiotensin II, vasopressin, norepinephrine, or endothelin, to a receptor with seven membrane-spanning domains. This receptor is linked to the activated G_q-protein subunit, which stimulates phosphatidylinositol-specific PLC (PI-PLC) to produce inositol 1,4,5,-triphosphate, which acts to cause release of Ca^{2+} from the SR, activating the actin-myosin system in the smooth muscle cells, producing vasoconstriction. Another second messenger, 1,2-diacylglycerol, is also produced, which goes on to activate protein kinase C, which in turn has a role in mitogenesis and thus the proliferation of smooth muscle cells. There are many isozymes of PLC; the form implicated in this series of events is the $PLC_ß$ form. The PLCγ isoform is

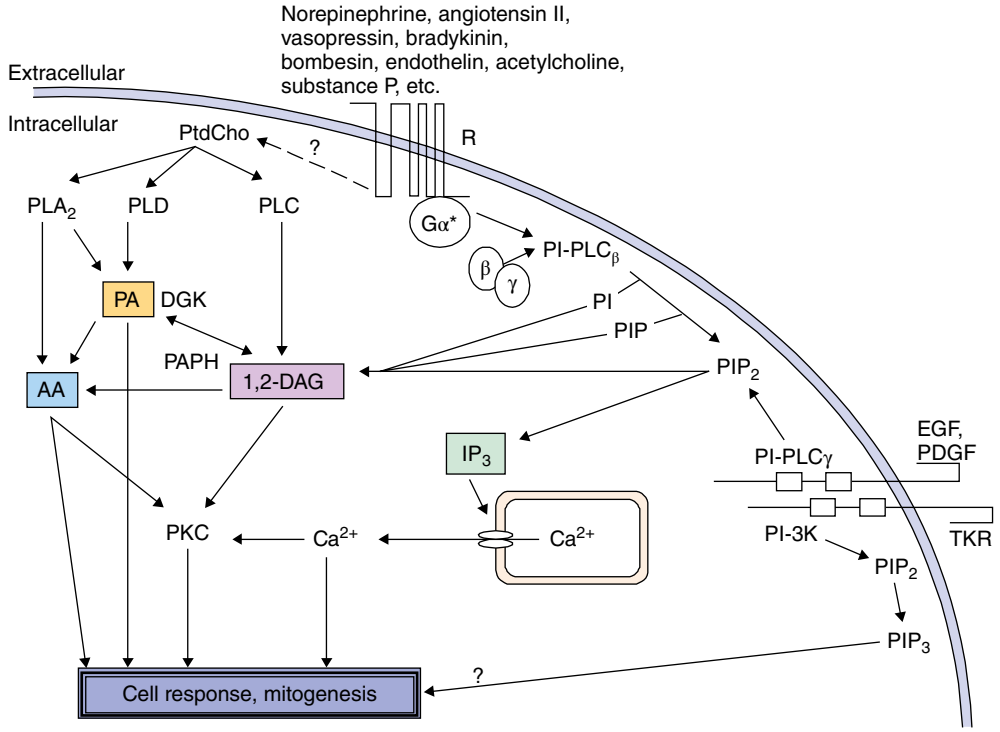


Figure 9.15 Phospholipase C system. Diagram summarizing the major receptor-activated pathways for the production of inositol 1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (1,2-DAG). The binding of an agonist to a receptor R with seven membrane-spanning domains results in the activation of the phosphatidylinositol-specific phospholipase Cß (PI-PLCß), whereas the stimulation of tyrosine kinase receptors (TKRs) by polypeptide growth factors will activate phosphatidylinositol-specific phospholipase Cγ (PI-PLCγ). Both pathways will result in the hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP2) and the formation of IP3 and 1,2-DAG. In addition, agonists that act on the heterotrimeric receptors may stimulate phosphatidylcholine (PtdCho) hydrolysis, and activation of tyrosine kinase receptors will stimulate the production of phosphatidylinositol 3,4,5-triphosphate (PIP3). AA, arachidonic acid; β, β subunits; DGK, diacylglycerol kinase; EGF, epidermal growth factor; G*, activated G-protein subunit; PAPH, phosphatidic acid phosphohydrolase; PDGF, platelet-derived growth factor; PI, phosphatidylinositol; PIP, phosphatidylinositol 4-phosphate; PI-3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLA_2, phospholipase A_2; PLD, phospholipase D. (Source: Izzard et al. [120]. Reproduced with permission of Elsevier.)

activated when cell growth factors such as platelet-derived growth factors bind to their receptors on the cell surface and active tyrosine kinases. This results in the production of phosphatidylinositol 3,4,5-triphosphate, which is also implicated in mitogenesis.

Vasodilatation of the systemic circulation results from the formation of nitric oxide by nitrovasodilators, or by activation of ß$_2$-adrenergic receptors in the peripheral vasculature, both of which result in the activation of guanylate cyclase and the production of cGMP, which reduces intracellular Ca^{2+} concentrations, producing vasodilation [125].

The vascular beds in various peripheral tissues differ in the amount of local metabolic control of vascular tone. For example, pH has much more influence on the pulmonary circuit, with low pH leading to vasoconstriction and higher pH leading to vasodilatation, than in the vascular tone of other tissues. Local CO_2 concentration is much more important to central nervous system vasculature, with high levels leading to vasodilatation. A decrease in oxygen tension will often lead to vasodilatation, as adenosine is released in response to the decreased oxygen delivery; however, decreased oxygen tension increases tone in the pulmonary circulation. Autoregulation, or maintaining relatively constant blood flow over a wide range of arterial pressures, predominates in the cerebral circulation but is not as critical in other tissue beds. Autoregulation and CO_2 responsiveness are both blunted in the fetal and immature brain [126].

KEY POINTS: REGULATION OF VASCULAR TONE IN SYSTEMIC AND PULMONARY CIRCULATIONS

- The pulmonary vascular endothelium exerts major control of vascular tone and resistance, maintaining low resistance through complex pathways, including nitric oxide, prostaglandins, and cGMP.
- Systemic vascular tone and resistance are maintained in a higher resistance state than the pulmonary vascular circulation with more neurohormonal activation that includes the sympathoadrenal, renin-angiotensin-aldosterone, and phospholipase-C systems.
- Pathophysiologic derangements in vascular tone of pulmonary and systemic circulations have led to therapeutic approaches such as inhaled nitric oxide and endothelin receptor antagonists.

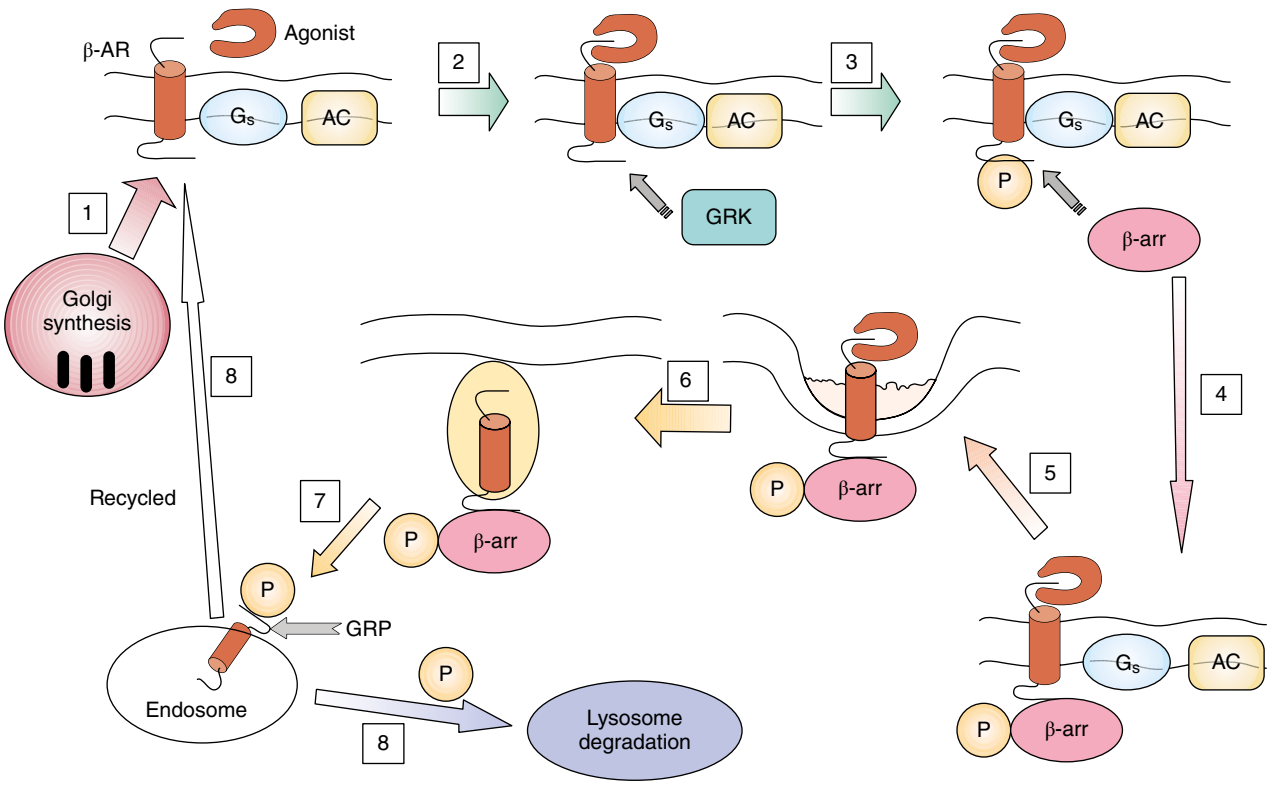


Figure 9.16 Desensitization and downregulation of the ß adrenoreceptor (ß-AR). 1, agonist binding; 2, phosphorylation of the ß-AR by G-protein-coupled receptor kinases (GRK); 3, ß-arrestin binds to the GRK-phosphorylated ß-AR, which is bound to the G_s protein. The receptor is then sequestrated to the endosomal compartment (4–7), to be dephosphorylated, and then either recycled back to the sarcolemma (8) or translocated to lysosomes for further degradation (8). AC, adenylate cyclase; GRP, G-protein-coupled receptor phosphatase; P, inorganic phosphate groups; ß-arr, ß-arrestin. (Source: Booker [69]. Reproduced with permission of John Wiley & Sons.)

Receptor signaling in myocardial dysfunction, CHD, and heart failure

A discussion of receptor signaling and calcium cycling in myocardial dysfunction is useful to serve as the basis for understanding many of the therapies discussed later in this text, and this section will focus on receptor physiology and calcium flux in three settings: acute myocardial dysfunction as seen after cardiac surgery and cardiopulmonary bypass, changes seen as responses to chronic cyanotic heart disease, and those seen with chronic congestive heart failure and cardiomyopathy.

Receptor signaling in acute myocardial dysfunction

Acute myocardial dysfunction, such as that sometimes seen after cardiopulmonary bypass, is often treated with catecholamines. These drugs are sometimes ineffective, especially when used in escalating doses. In children, the number and subtype distribution of ß-adrenergic receptors in atrial tissue is not affected by cardiac surgery with bypass; however, the activation of adenylate cyclase by isoproterenol is significantly reduced after bypass [127]. There is an uncoupling of ß receptors from the G_s – protein–adenylate cyclase complex. Desensitization to moderate or high doses of catecholamines may occur after only a few minutes of administration because increased cAMP concentrations result in uncoupling from the G_s protein [128].

Only a few minutes of high-dose catecholamine administration may result in the inactivation of the phosphorylated adrenergic receptors from sequestration. These receptors can be sequestered by endocytosis, in a process involving a protein called ß-arrestin, which binds to the receptor and clathrin, a sarcolemmal protein (Figure 9.16) [69]. These sequestered receptors may be either recycled back to the cell membrane surface or destroyed by lysosomes [129]. This permanent destruction and degradation of receptors occur after hours of exposure to catecholamines and is accompanied by decreased mRNA and receptor protein synthesis, resulting in a prolonged decrease in adrenergic receptor concentrations, which is reversed by decreasing exogenous catecholamines, but only as fast as new receptors can be synthesized.

Neonatal hearts may exhibit a different response to the acute or prolonged administration of catecholamines. Instead of desensitization, neonatal animal models demonstrate an enhanced ß-adrenergic receptor response, accompanied by an increase in adenylate cyclase activity [130]. Desensitization as described earlier occurs later in development. The exact translation of these data to humans is not clear.

Treatment with catecholamines may also increase the concentration of G_i protein subunits, decreasing the sensitivity of the ß-adrenergic receptor. This relative decrease in the ratio of G_s to G_i protein subunits has been demonstrated in

rat and dog models [131, 132]. Another possible mechanism of catecholamine-induced desensitization of the neonatal myocyte was demonstrated in a rat model, where prolonged exposure to norepinephrine caused an initial increase in functional L-type Ca^{2+} channels on the sarcolemmal membrane. Continued exposure caused a decrease in L-type Ca^{2+} channel mRNA to 50% of control values [133]. SERCA concentrations are reduced with chronic norepinephrine administration in the dog [134]. Finally, exposing adult or neonatal rat myocytes to high concentrations of catecholamines for 24 hours leads to increased apoptosis of myocardial cells, a genetically programmed energy-dependent mechanism for cell death and removal [135, 136]. This effect was mediated through ß-adrenergic receptors in the adult model and α receptors in the neonatal model.

All of these studies provide the theoretical basis for the argument that the administration of catecholamines to patients with acute myocardial dysfunction should be limited in dose and duration. Obviously, this is difficult to accomplish in the setting of weaning a hemodynamically unstable patient from cardiopulmonary bypass. Strategies that may limit catecholamine dose include administering low doses of catecholamines together with phosphodiesterase inhibitors, as well as adding corticosteroids, tri-iodothyronine, and vasopressin [137].

Receptor signaling in CHD

In the past decade, new information concerning adrenergic receptor signaling in patients with CHD has come to light. A study of 71 infants and children undergoing cardiac surgery used tissue from the right atrial appendage to study ß-adrenergic receptor density, distribution of $ß_1$ and $ß_2$ receptor subtypes, and coupling to adenylate cyclase [138]. This study found that patients with severe, or poorly compensated acyanotic (e.g. congestive heart failure) or cyanotic (e.g. severe cyanosis) disease had significantly reduced ß-adrenergic receptor densities. Outside of the newborn period, this down-regulation was $ß_1$-selective, but in newborns with critical aortic stenosis or transposition of the great arteries, there was additional significant downregulation of the $ß_2$ subtype. In patients with the tetralogy of Fallot, those treated with propranolol had a significant increase in the number and density of ß-adrenergic receptors, when compared with untreated patients. Beta-adrenergic receptor downregulation was correlated with increased circulating norepinephrine levels. Finally, in severely affected patients, adenylate cyclase activity was reduced, demonstrating a partial decoupling, as noted earlier. Other studies have determined that symptomatic tetralogy of Fallot patients (i.e. those with cyanotic spells) have a significantly greater number of ß-adrenergic receptors in their right ventricular outflow tract muscle, and their adenylate cyclase activity was greater than that in patients without cyanotic spells [73]. Alpha-1-adrenergic receptors are also affected by CHD. A study of atrial tissue excised at the surgery in 17 children evaluated α- vs. ß-adrenergic receptor stimulation with pharmacologic agents. The α component was responsible for 0–44% of the inotropic response, and ß stimulation for 56–100% of the response, with the degree of right ventricular hypertrophy and pressure load correlating with the amount of stimulation found [139].

Receptor signaling in congestive heart failure and cardiomyopathy

Like adults with heart failure, children with congestive heart failure due to chronic left-to-right shunting and volume overload of the heart have elevated levels of circulating norepinephrine. This leads to a downregulation in ß-adrenergic receptor density [140]. The degree of elevation of pulmonary artery pressure and amount of left-to-right shunting correlates with the plasma catecholamine levels and is inversely correlated with ß-adrenergic receptor density. All of these abnormalities return to normal levels after corrective surgery. The degree of receptor downregulation in congestive heart failure is correlated with postoperative morbidity in infants and children. Children with an intensive care unit stay of greater than 7 days or those who died during the early postoperative period (nine of 26) had significantly less $ß_1$ and $ß_2$ mRNA gene expression than those who had better outcomes [141]. In addition, the children receiving propranolol for treatment of their congestive heart failure had higher ß-adrenergic receptor mRNA levels and tended to have improved outcomes. Finally, children with dilated cardiomyopathy also have a reduced response to catecholamines, with one study showing no significant increase in ejection fraction during the dobutamine stress test, with an infusion of dobutamine at 5 and then 10 µg/kg/min [142]. Generally, studies in excised right atrial tissue in infants and children with CHD or cardiomyopathy demonstrate decreased density of $ß_1$ and $ß_2$ receptors, and decreased downstream adenylate cyclase function, with larger decreases associated with worse ventricular function [143].

This has been a brief discussion of receptor signaling in pediatric heart disease. This emerging field has many implications for treatment strategies, and the reader is referred to excellent reviews for more detailed information on this subject [144].

KEY POINTS: RECEPTOR SIGNALING IN MYOCARDIAL DYSFUNCTION, CHD, AND HEART FAILURE

- High catecholamine doses in acute myocardial dysfunction can desensitize the myocardium through uncoupling of G-protein adenylate cyclase complex, and sequestration of β-adrenergic receptors.
- Significant cyanotic or acyanotic CHD with heart failure can result in down-regulation of β-adrenergic receptors in neonatal or infant myocardium.
- Longstanding decreased ventricular function is often associated with the decreased density of β-adrenergic receptors and decreased adenylate cyclase function.

Myocardial preconditioning

Myocardial preconditioning refers to the finding that repeated, brief exposures of the myocardium to ischemia, volatile anesthetics, or other stresses induces a protective

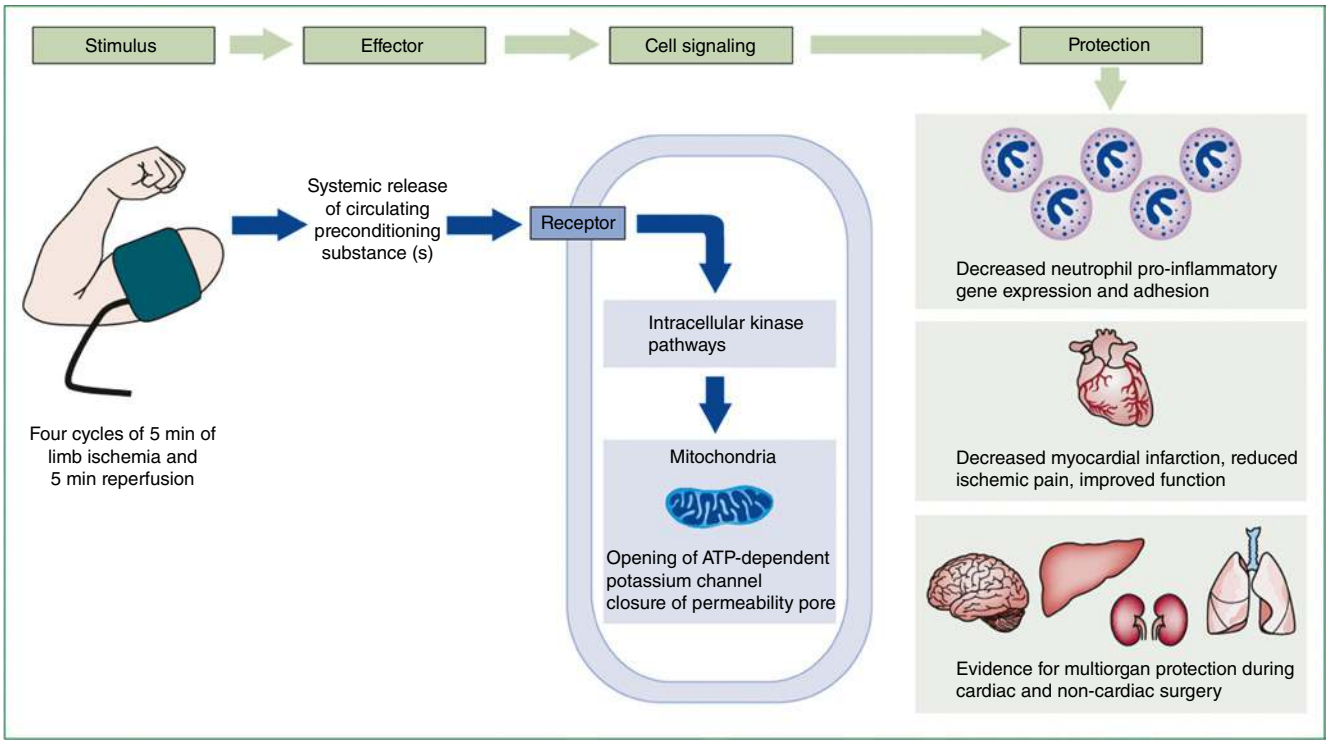


Figure 9.17 Biological effects of remote ischemic preconditioning. Transient ischemia of the arm liberates a circulating effector that induces remote cellular adaptation to a subsequent, extended and potentially lethal period of ischemia in remote tissues. (Source: Kharbanda et al. [146]. Reproduced with permission of Elsevier.)

effect to a later (i.e. 12–24 hours), more prolonged, ischemic insult, resulting in decreased myocardial infarction size and improved myocardial function after the insult [145]. Chronic cyanosis also induces a similar protective effect in the myocardium, although the effect size is smaller and more long-lasting (i.e. beyond 24 hours). Another mechanism is remote ischemic preconditioning (RIPC), in which ischemia is produced in a tissue bed remote to the myocardium, for example, skeletal muscle of the arm or leg by repeated inflation of a blood pressure cuff which is thought to liberate as yet uncharacterized neurohumoral or hormonal substances that can protect the myocardium (Figure 9.17) [146]. The mechanisms of myocardial preconditioning are complex but are thought to involve the release of various neurohormonal agents and peptides such as adenosine, bradykinin, and nitric oxide via a cGMP-dependent mechanism, which then triggers a series of signal transduction events within the cardiomyocyte that confer a "memory" effect that protects the myocardium from future ischemic insults. The signal transduction effects include PKC, tyrosine kinases, mitogen-activated protein kinases, glycogen synthase kinase 3β, and other enzymes [147]. This series of events allows activation of mitochondrial and sacrolemmal K_{ATP} channels, which leads to the preconditioning by elusive mechanisms. One recently discovered candidate for this end effector is the mitochondrial permeability transition pore (MPTP) [147]. This is a non-specific channel that spans both mitochondrial membranes, and when opened for a prolonged period results in a dissipation of mitochondrial electrical potential, inhibition of ATP synthesis, and ultimately mitochondrial swelling, rupture, failure of cellular energy metabolism, and cell death. Agents and stimuli that confer myocardial preconditioning have been found to keep the MPTP closed, thus possibly elucidating further the subcellular mechanisms involved.

Several recent pediatric cardiac surgery studies have been published elucidating the potential effects of myocardial preconditioning, which could have the beneficial effect of ameliorating the myocardial stunning effect seen in operations on infants with long aortic cross-clamp times [148]. In a study of 90 infants randomized to sevoflurane, propofol, or midazolam anesthesia for maintenance, plus a sufentanil infusion for analgesia, patients receiving sevoflurane had a very strong trend toward lower troponin T concentrations in the first 24 hours after surgery, potentially signifying less myocardial injury due to the pre-bypass exposure to sevoflurane [150]. Remote ischemic preconditioning produced by inflating a blood pressure cuff on a lower extremity to produce a 5-minute period of limb ischemia, for four cycles before cardiopulmonary bypass, was studied in 37 children undergoing cardiac surgery. Patients who underwent RIPC had lower peak troponin I levels (17 vs. 22 μg/L, $P = 0.04$), and lower inotrope score in the RIPC group at 3 and 6 hours post-bypass [149]. This interesting phenomenon of RIPC may work via modulation of the inflammatory response through some as yet unknown humoral mechanism. Some recent small controlled trials of RIPC in children measured inflammatory and myocardial injury markers such as tumor necrosis

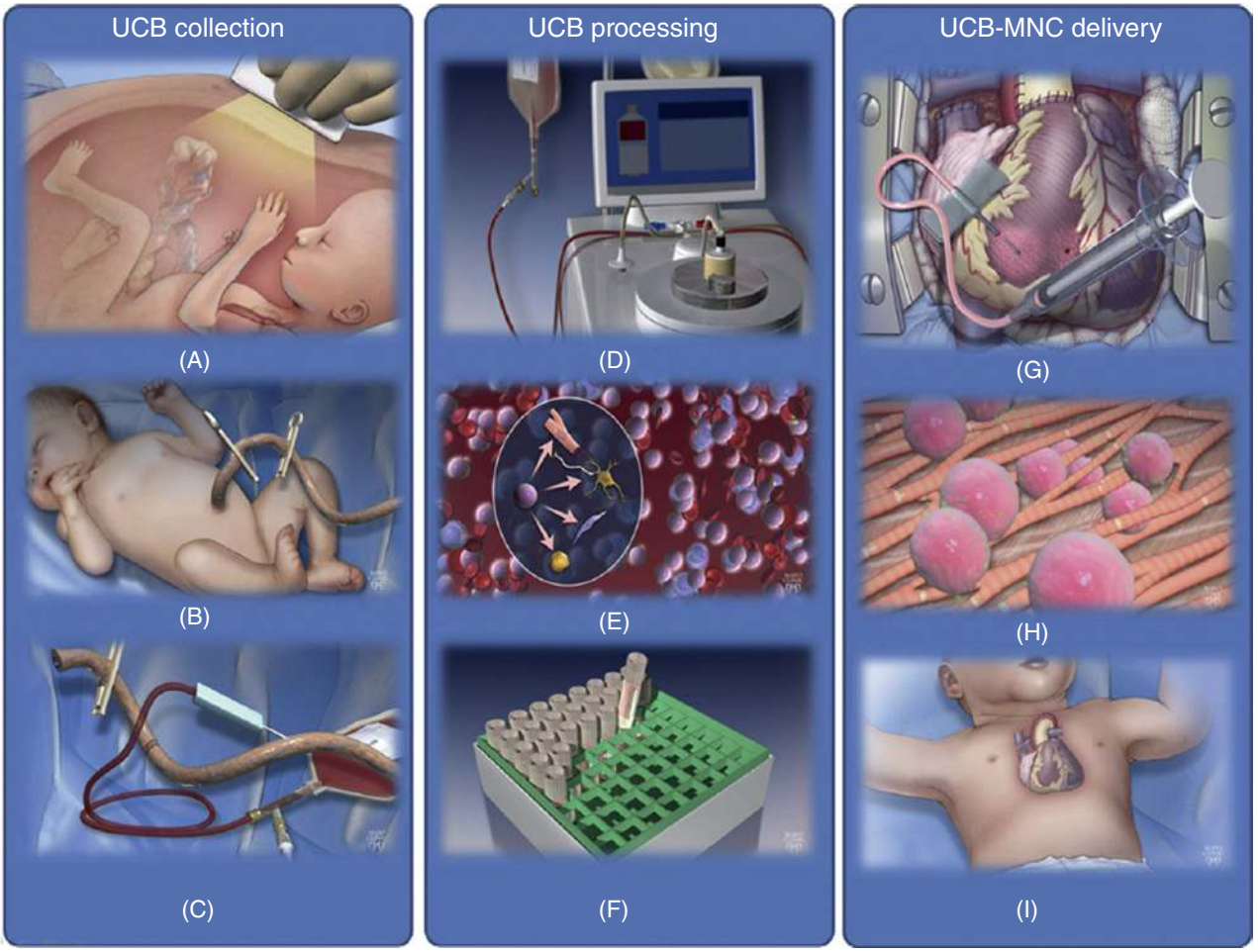


Figure 9.18 Diagnosis of hypoplastic left heart syndrome is established by a fetal echocardiogram (A). Umbilical cord blood (*UCB*) collection kit is sent to the family before birth and used to maximize collection volume (B and C). UCB is collected by local hospital staff, packaged, and transported by a dedicated courier to a specialized laboratory where the sample is processed to isolate the mononuclear cell product via Ficoll density gradient separation (D and E). The final cell-based product is cryopreserved in sterile 2 mL cryovials with 10% dimethyl sulfoxide at a predetermined concentration and stored in the vapor phase of liquid nitrogen (F). After the completion of superior cavopulmonary anastomosis, the UCB-derived mononuclear cells (*UCB-MNC*) are directly injected into the subepicardial myocardium (G). These autologous cells are transiently residing and contributing only to the paracrine influence within the myocardial microenvironment (H) establishing the safety and feasibility of this novel experimental therapy (I). (Source: Burkhart et al. [158]. Reproduced with permission of Elsevier.)

factor-alpha and interleukins (ILs). Several of these studies demonstrated decreases in creatine kinase, inflammatory mediators IL-8 and -10, heat shock protein, and cardiac enzymes creatine kinase and troponin I with RIPC. However, none of these studies demonstrated a clinical difference in ventilation time, intensive care unit stay, end-organ dysfunction, or death [151–154]. Thus, it would appear that despite the initial enthusiasm for this relatively simple clinical intervention, the studies to date demonstrate no clinical benefit. The exact mechanisms of RIPC are still not completely elucidated, and the small muscle mass of infants and children compared with adults, the different clinical approaches to anesthetic agent and corticosteroid use, and the small numbers of patients studied to date may prevent conclusive data. A large single-center, blinded, randomized controlled trial published in 2014 by McCrindle and colleagues studied 299 children aged neonate to 17 years.

[155] The RIPC group received four 5-minute cuff inflations on the thigh of 15 mmHg above systolic pressure before bypass. There were no differences in the primary outcome of the duration of hospital stay, nor in secondary outcomes of the duration of mechanical ventilation or hospital stay. There were also no differences in physiologic or laboratory outcomes, including markers of cardiac, hepatic, renal, or hemotologic dysfunction; inflammatory markers, or physiologic measures of hemodynamic instability. An international multicenter controlled trial of RIPC in the study of 5,401 adult patients with suspected ST-elevation myocardial infarction (STEMI) also did not show any difference in cardiac death or hospitalization for heart failure [156]. RIPC thus would appear to be an example of a promising therapy in the preclinical setting and small clinical studies, but when subjected to rigorous study design with an adequate sample size, does not change clinically important outcomes.

KEY POINTS: MYOCARDIAL PRECONDITIONING

- Myocardial preconditioning is a complex phenomenon by which repeated brief exposure of the myocardium to ischemia or other stresses induces a protective effect to later ischemic insults.
- The mitochondrial permeability transition pore is a common pathway for the various forms of ischemic preconditioning, staying closed and preventing mitochondrial failure.
- Remote ischemic preconditioning produced by inflation of a blood pressure cuff on a limb before CPB may reduce some inflammatory and ischemic cell death markers, but does not improve clinical outcomes.

Stem cell and other cell-based therapy for congenital heart disease

A very interesting and promising approach to regeneration and repair of cardiac myocytes damaged by chronic heart failure due to congenital heart disease, or cardiomyopathy is the administration of autologous or allogeneic stem cells, or other pre-differentiated cells types, into the myocardium [157]. Hypoplastic left heart syndrome (HLHS) patients remain a challenging group because the systemic right ventricle often fails even with technically perfect surgery and a stable postoperative course after the Norwood stage I palliation. Autologous cells derived from a mononuclear population of umbilical cord blood (UCB-MNC) at birth can assimilate into the myocardium. After processing to ensure sterility and a uniform population of mononuclear cells, umbilical cord blood-derived mononuclear cell (**UCB-MNC**) has been tested in an ongoing trial by injecting them directly into the right ventricular myocardium during the Stage II (bidirectional cavopulmonary anastomosis) operation for HLHS. A dose of 1–3 million umbilical cord-derived mononuclear cells per kilogram is injected [158] (Figure 9.18). Vicenti and colleagues published results of a phase II study of seven HLHS patients injected with these cells, compared retrospectively to 17 controls [159]. By 6 months postoperatively, treated patients had a 3% increase in right ventricular contractility vs. a 5% decrease for controls ($p = 0.03$). Somatic growth was also improved in the treated patients, up to 63rd percentile vs. decrease to the 8th percentile in the control group ($p = 0.02$). Sano and colleagues reported intracoronary infusion of cardiosphere-derived cells (CDC), a type of cardiac progenitor cells, harvested from the patient at the time of a previous Norwood stage I/II surgery, after stage II or stage III repair in 41 HLHS patients compared to 60 controls [160]. Two years after infusion, survival between groups was not different, but CDC treated patients had lower incidence of late heart failure ($p = 0.022$), adverse events ($p = 0.013$), and catheter interventions ($p = 0.005$). In patients with heart failure with reduced ejection fraction, mortality and late complications were improved in CDC treated patients vs. controls. Interestingly, the paracrine hypothesis is thought to be the predominant mechanism of action of the UCB-MNC and CDC. These cells reside only transiently in the myocardium, but can secrete factors that stimulate endogenous cellular proliferation, while shifting tissue remodeling pathways away from a fibrotic/inflammatory response, to one that can activate endogenous repair mechanisms. Several trials are ongoing and could provide a relatively simple method to improve cardiac function in single ventricle infants. Safety profile is reported to be excellent in the follow-up to date.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

21 Sander TL, Klinkner DB, Tomita-Mitchell A, Mitchell ME. Molecular and cellular basis of congenital heart disease. Pediatr Clin N Am 2006;53:989–1009. An overview of the emerging knowledge of the genetic, molecular, and cellular bases for the structural development of congenital heart disease as well as the pathophysiology related to cardiac function.

43 Harvey PA, Leinwand LA. The cell biology of disease: cellular mechanisms of cardiomyopathy. J Cell Biol 2011;194:355–65. A comprehensive modern review of established and new cellular mechanisms of inherited and acquired cardiomyopathy, with outstanding illustrations.

46 Sheikh F, Ross RS, Chen J. Cell-cell connection to cardiac disease. Trends Cardiovasc Med 2009;19:182–90. A review article focusing on anatomy and function of the intercalated disc, which is the complex structure providing the electrical, biochemical, and structural connections between cardiac myocytes enabling coordinated function of the heart. New concepts are stressed, along with the contribution of genetic and acquired abnormalities of the cell-to-cell connections to cardiac disease states.

68 Booker PD. Pharmacological support for children with myocardial dysfunction. Paediatr Anaesth 2002;12:5–25. A classic review article in the pediatric anesthesia literature laying the receptor and cellular function foundation for approaches to inotropic treatment. The pharmacologic approaches are reviewed in the latter half of the paper.

104 Prakash YS, Seckin I, Hunter IW, et al. Mechanisms underlying greater sensitivity of neonatal cardiac muscle to volatile anesthetics. Anesthesiology 2002;96:893–906. A now classic review article summarizing the developmental differences in neonatal vs. more mature cardiac muscle, and presenting the animal model experiments that form the basis for greater depression of volatile anesthetics in the neonatal heart.

110 Boegehold MA. Endothelium-dependent control of vascular tone during early postnatal and juvenile growth. Microcirculation 2010;17:394–406. A comprehensive review of well-established and emerging concepts of the endothelial milieu and its control of both systemic and pulmonary vascular tone during the neonatal and young infant period.

113 Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. Physiol Rev 2010;90:1291–335. A very extensive review of the well-established principles of regulation of the pulmonary circulation in fetal and neonatal life, as well as newer and emerging concepts. Outstanding figures emphasizing new concepts.

142 Buijs EA, Danser AH, Meijer NI, Tibboel D. Cardiovascular catecholamine receptors in children: their significance in cardiac disease. J Cardiovasc Pharmacol 2011;58:9–19. A review of published human studies of catecholamine receptors studied in excised cardiac tissue in cardiovascular disease, emphasizing changes from normal hearts, and implications for pharmacological therapies.

143 Schwartz SM, Duffy JY, Pearl JM, Nelson DP. Cellular and molecular aspects of myocardial dysfunction. Crit Care Med 2001;29:S214–9. An overview of cellular and molecular derangements in acquired myocardial dysfunction, with implications for pharmacologic treatment.

155 McCrindle BW, Clarizia NA, Khaikin S, et al. Remote ischemic preconditioning in children undergoing cardiac surgery with cardiopulmonary bypass: a single-center double-blinded randomized trial. J Am Heart Assoc 2014;3:e000964. A large randomized trial of 299 infants and children undergoing congenital heart disease surgery randomized to remote ischemic precondition regimen prebypass vs. sham treatment. There was no difference between groups in any clinical or laboratory outcome.

160 Sano T, Ousaka D, Goto T, et al. Impact of cardiac progenitor cells on heart failure and survival in single ventricle congenital heart disease. Circ Res 2018;122:994–1005. A trial of cardiosphere derived stem cells in hypoplastic left heart syndrome patients injected after stage II or III surgery. Improved heart failure symptoms, cardiac function, and somatic growth occurred in the treated patients 2 years after infusion of the cells.

CHAPTER 10

Anesthetic Agents and Their Cardiovascular Effects

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Introduction

A wide variety of anesthetic regimens are used for patients with congenital heart disease (CHD) undergoing cardiac or non-cardiac surgery, procedures in the cardiac catheterization laboratory, or other diagnostic or therapeutic procedures such as magnetic resonance imaging (MRI). The goal of all of these regimens is to produce general anesthesia or adequate sedation while preserving systemic cardiac output (CO) and oxygen delivery. Many of these patients have a limited cardiac reserve, and if a cardiac arrest or other adverse cardiac event occurs, successful resuscitation is less frequent than in patients with normal hearts [1]. Thus, intelligent selection of regimen and dosage, with the patient's unique pathophysiology in mind, along with anesthetic requirements for the particular procedure they are undergoing, is essential. This chapter reviews the effects on hemodynamics and myocardial contractility of anesthetic agents and muscle relaxants commonly used for patients with CHD.

Volatile agents

Although halothane is no longer available in the US, it is still used in some parts of the world, and it serves as the basis for comparison with newer agents because of the number of studies of its hemodynamic effects in children with and without heart disease. Therefore, data concerning halothane will be presented in this section. *In vitro* studies of effects on contractility in isolated adult human atrial fibers indicate that direct myocardial contractility depression is at its greatest with halothane and that sevoflurane is equal to isoflurane and desflurane [2] (Figure 10.1). These studies of myocardium reveal that the differences among these agents occur primarily from differing effects on calcium flux through L-type Ca^{2+} channels, both transsarcolemmal and in the sarcoplasmic reticulum (SR). Halothane reduces Ca^{2+} flux through the sarcolemma more than isoflurane, with the net result of less intracellular Ca^{2+} available to bind to the troponin–actin–myosin complex, which produces myocyte contraction. Another mechanism of myocardial depression is that halothane, but not isoflurane, directly activates ryanodine-sensitive SR Ca^{2+} channels, thereby reducing Ca^{2+} storage in the SR and making it less available for release during contraction. The effects of sevoflurane and desflurane on Ca^{2+} flux are similar to those of isoflurane [2].

It is important to note that infants from the newborn period up to an age of approximately 6 months exhibit an exaggerated degree of depression of myocardial contractility and blood pressure in response to all volatile agents, but especially halothane [3, 4] (Figure 10.2). This is probably due to the immaturity of the Ca^{2+} release and reuptake system, necessitating higher levels of free cytosolic Ca^{2+} to be available to bind to the troponin–actin–myosin complex to produce myocyte contraction [5]. Sevoflurane, and to a greater extent halothane, interferes with both L-type Ca^{2+} channel and Na^+/Ca^{2+}

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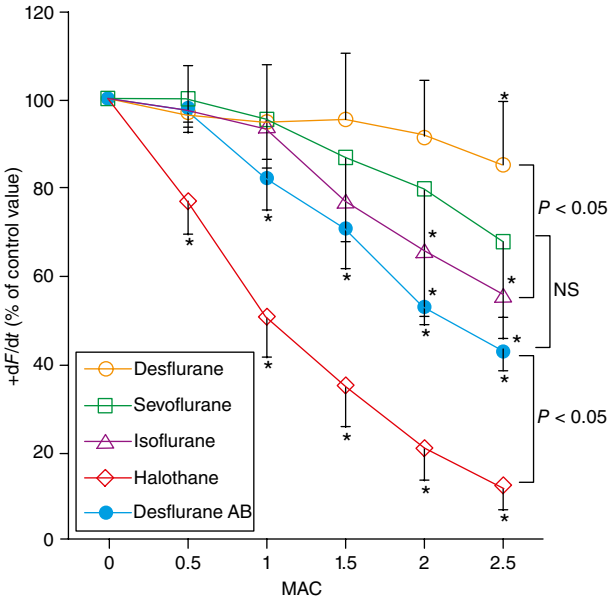


Figure 10.1 Force of contraction over time (+d*F*/d*t*) of isolated adult human atrial trabeculae in response to 0–2.5 minimum alveolar concentration (MAC) anesthetics. Desflurane AB = desflurane in the presence of α- and ß-receptor blockade. Halothane depresses contractility significantly more than all other agents at every MAC. (Source: Hanouz et al. [2]. Reproduced with permission of Wolters Kluwer Health, Inc.)

exchanger Ca^{2+} flux at the plasmalemmal membrane more in neonatal than in adult rat myocytes [6]. The volatile anesthetics interfered with Ca^{2+} release from the SR more in adult rat myocytes. Ca^{2+} release from the SR is thought to be less contributory to cytosolic Ca^{2+} levels in neonatal rat myocytes [7]. This information provides a mechanism for what is commonly observed clinically.

The effects of volatile agents on systemic vascular resistance (SVR), as measured by arterial blood pressure, differ between agents. Ca^{2+} flux in the smooth muscles of arterioles is reduced by all of these agents, resulting in less resting tone, and thus lower blood pressure and vascular resistance. Halothane exhibits the most pronounced reduction of blood pressure, due to the combination of reduction in arterial tone, as well as the more pronounced depression of myocardial contractility. Isoflurane and sevoflurane lower blood pressure primarily through a reduction in SVR [8].

Sevoflurane has largely replaced halothane throughout most of the world for induction and maintenance of anesthesia. The Pediatric Perioperative Cardiac Arrest Registry data demonstrated a decrease in anesthetic medication-related cardiac arrests, from 37% of the total in 1994–1997 to 18% in 1998–2004; the authors primarily attributed this decrease to the less frequent use of halothane, leading to fewer arrests, particularly in young infants [9].

In patients with CHD, several studies have been performed comparing newer agents with halothane. A study using transthoracic echocardiography comparing halothane, isoflurane, and sevoflurane [8] in 54 children with two-ventricle CHD (Table 10.1, Figure 10.3) reported that 1 and 1.5 MAC (minimum alveolar concentration) halothane caused significant myocardial depression, resulting in a decrease in mean arterial pressure (MAP, decline of 22 and 35%, respectively), ejection fraction (EF, decrease of 15 and 20%, respectively) and CO (decrease of 17 and 21%, respectively) in patients aged 1 month to 13 years undergoing cardiac surgery. Sevoflurane maintained both CO and heart rate (HR) and had less profound hypotensive (MAP decrease of

Table 10.1 Hemodynamic changes in response to four anesthetic regimens in 54 children with congenital heart disease with two ventricles

Measured and calculated hemodynamic and echocardiographic variables									
Agent	**MAC**	**HR (beats/min)**	**(mmHg)**	**EF (%)**	**SF (%)**	**SVI (mL/m²)**	**LVEDVI (mL/m²)**	**CI (L/min/m²)**	**SVRI (dyn s/cm⁵/m²)**
Halothane	0	129±22	77±15	63±9	40±5	36±16	44±19	4.49±1.87	1425±622
	1	130±19	60±11[a]	54±12[a]	32±7[a,b]	28±11[a]	38±14	3.47±1.17	1331±529
	1.5	129±17	49±12[a]	50±13[a]	30±8[a,b]	26±11[a]	39±12	3.34±1.36[a]	1132±503[a]
Sevoflurane	0	123±32	67±8	68±11	44±7	56±41	37±15	6.91±4.32	1014±653
	1	126±26	58±13[a]	62±9	39±7	52±31	36±18	6.59±4.04	883±592
	1.5	128±25	58±13[a]	58±10[a]	39±9	46±26	35±14	5.78±3.06	782±390
Isoflurane	0	112±27	69±12	63±7	39±5	46±2	46±24	4.96±2.74	1377±809
	1	125±16[a]	54±9[a]	62±8	37±4	39±17	40±17	4.82±2.20	1022±601[a]
	1.5	128±13[a]	50±9[a]	59±9	36±5	39±17	42±19	4.59+2.12	950±513[a]
Fentanyl–midazolam	0	106±22[c]	66±8	63±6	40±6	46±34	54±25	5.16±4.39	1261±644
	1	87±19[a,d]	59±11[a]	60±7	39±5	42±30	47±25	3.79±3.05[a]	1540±806
	1.5	82±18[a,d]	56±11[a]	59±7	38±7	43±30	52±24	3.67±2.99[a]	1559±875

Source: Rivenes et al. [8]. Reproduced with permission of Wolters Kluwer Health, Inc.

All values are means ± SD.

CI, systemic cardiac index; EF, ejection fraction; HR, heart rate; LVEDVI, left ventricular end-diastolic volume index; MAP, mean arterial pressure; SF, shortening fraction; SVI, stroke volume index; SVRI, systemic vascular resistance index.

[a] $P < 0.05$, one-way analysis of variance (ANOVA), different from 0 minimum alveolar concentration (MAC) within the same anesthetic group.

[b] $P < 0.05$, two-way ANOVA, halothane vs. sevoflurane and fentanyl-midazolam at 1 and 1.5 MAC.

[c] $P < 0.05$, two-way ANOVA, fentanyl–midazolam vs. halothane at 0 MAC.

[d] $P < 0.05$, two-way ANOVA, fentanyl–midazolam vs. halothane, sevoflurane, and isoflurane at 1.0 and 1.5 MAC.

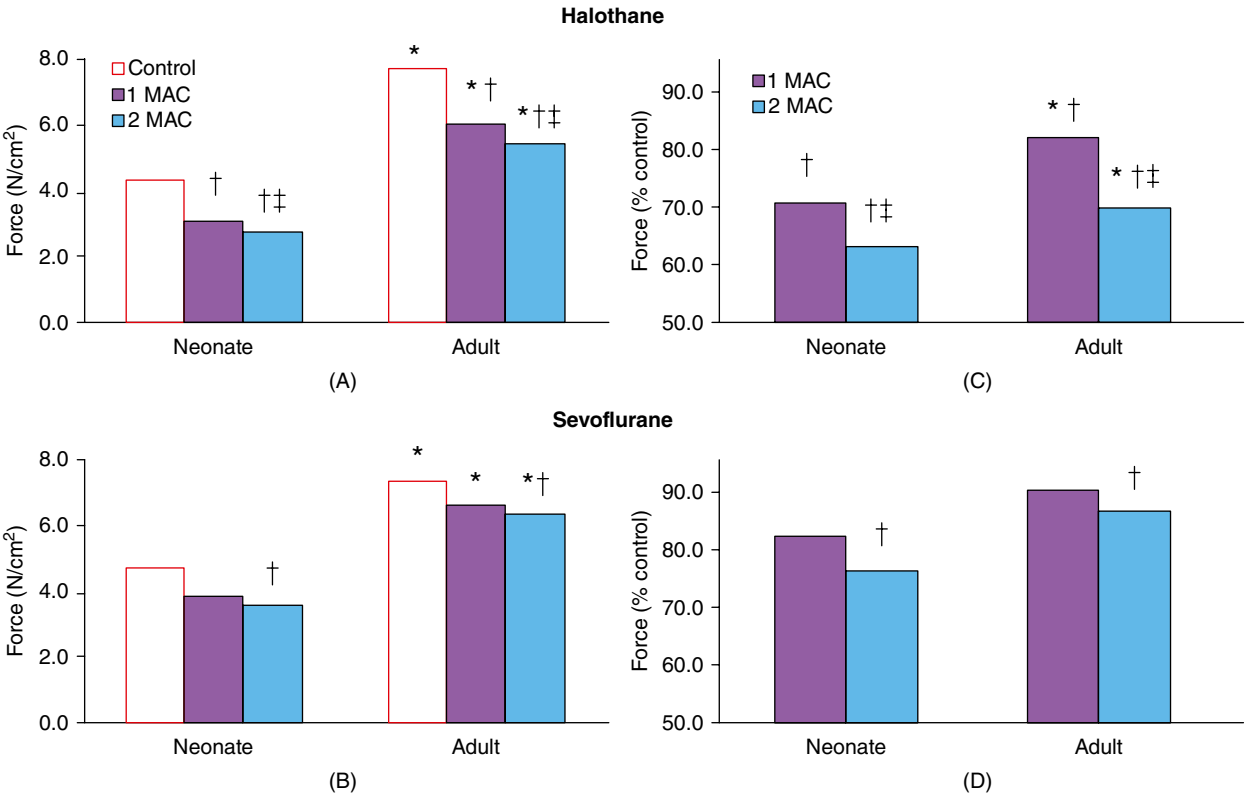


Figure 10.2 Force of contraction (N/cm^2) in neonatal vs. adult rat ventricular trabecular muscle. Baseline force of contraction is greater in adult tissue, and both halothane and sevoflurane depress contractility more in the neonatal than in adult ventricular muscle. Halothane depresses contractility to a greater extent in both age groups. Panels (A and B) report raw data, while panels (C and D) express results as a percentage of baseline contractility. *Indicates a significant difference between ages ($P < 0.05$; $n = 12$ for controls, and $n = 6$ for all other groups). †Indicates a significant difference between control and halothane groups. ‡Indicates a significant difference between 1 and 2 minimum alveolar concentration (MAC) anesthetic. (Source: Prakash et al. [4]. Reproduced with permission of Wolters Kluwer Health, Inc.)

13 and 20% at 1 and 1.5 MAC, respectively) and negative inotropic (EF preserved at 1 MAC, 11% decrease at 1.5 MAC) effects than halothane. Isoflurane, at concentrations as high as 1.5 MAC, preserved CO and EF, caused less suppression of MAP (22 and 25%) than halothane, increased HR (17 and 20%), and decreased SVR (20 and 22%).

Russell and colleagues [10] compared sevoflurane to halothane in the pre-bypass period in 180 children with a variety of cardiac diagnoses, including 14 with single-ventricle physiology and 40 with tetralogy of Fallot (TOF). The incidence of significant hypotension, bradycardia, and arrhythmia requiring drug treatment with atropine, phenylephrine, epinephrine, or ephedrine was higher with halothane (two events per patient vs. one with sevoflurane). Serum lactate also increased slightly with halothane.

In a randomized crossover comparison study of 1 MAC isoflurane vs. sevoflurane, Dalal and colleagues studied 10 children with a variety of CHD, including both single- and two-ventricle diseases [11]. Stroke volume, EF, and cardiac index were determined for the systemic ventricle using cardiac MRI techniques. There were no differences between agents for these parameters, or differences in MAP or HR in this small study.

The effects of these agents on pulmonary (Qp) and systemic blood flow (Qs) in 30 biventricular patients with left-to-right shunts (secundum ASD, VSD) have also been assessed. Halothane, isoflurane, and sevoflurane did not change Qp:Qs as measured by echocardiography [12].

Wang and colleagues assessed differences in HR, cardiac rhythm, and blood pressure in 55 infants aged 2–12 months during 8% sevoflurane induction [13]. Twenty-nine had increased pulmonary blood flow (PBF) (atrial septal defect [ASD], ventricular septal defect [VSD], patent ductus arteriosus [PDA]), and 26 had decreased PBF (TOF, pulmonic stenosis). The first 10 minutes of the anesthetic were assessed, and differences between groups compared. HR decreased from baseline in both groups, with a greater decrease in patients with decreased PBF. Blood pressure decreased significantly in the increased PBF group but was unchanged in the patients with decreased PBF. Junctional rhythm was observed in one patient in the increased PBF group.

Patients with a single functional ventricle comprise an increasing proportion of patients undergoing anesthetics for both cardiac and non-cardiac surgery, and studies of the hemodynamic effects of anesthetic agents are limited. Ikemba and colleagues [14] studied 30 infants with a single functional ventricle immediately before their bidirectional cavopulmonary connection, randomized to receive sevoflurane at 1 and 1.5 MAC or fentanyl/midazolam at equivalent doses. Myocardial performance index (MPI), a transthoracic echocardiographic measurement of combined systolic and diastolic ventricular function that can be applied to single-ventricle

patients, was not changed with any of these regimens when compared with baseline, indicating that either sevoflurane or fentanyl/midazolam can be used in this population to maintain hemodynamic stability.

The effect of sevoflurane on systolic ventricular function has been studied in specific populations of CHD patients. Muyskens and colleagues [15] performed a retrospective review of patients with repaired Tetralogy of Fallot (rTOF) undergoing cardiac magnetic resonance imaging (CMR). After propensity score matching, the rTOF patients who required general anesthesia with maintenance sevoflurane (range 0.83–2.83%) were found to have a significant decrease in the CMR-derived left ventricular ejection fraction (49 vs. 56%) and CMR-derived right ventricular ejection fraction (41 vs. 48%). Elhoff and colleagues [16] assessed changes in ventricular function during 17 instances of sevoflurane-based general anesthesia for pediatric heart transplant recipients undergoing cardiac catheterization with endomyocardial biopsies. A baseline, pre-anesthetic echocardiogram was obtained. A significant decrease in ventricular function from baseline, as measured by repeat echocardiography was noted after attainment of a stable maintenance phase of general anesthesia with sevoflurane (MAC 0.7–1.0). There was, however, no consistent evidence of alteration of diastolic function under general anesthesia.

In normal children, desflurane commonly produces tachycardia and hypertension during the induction phase, followed by a slight reduction in HR and systolic blood pressure during steady state at 1 MAC anesthetic level [17, 18]. There are no reports of its hemodynamic profile in patients with CHD. In a study of 47 children (mean age 12.8 years) undergoing electrophysiological study for supraventricular tachycardia (SVT), desflurane allowed for induction of the SVT in all patients and demonstrated no clinically important differences in any electrophysiologic measurement, as compared with a fentanyl-based anesthetic [19]. The very low arrhythmogenic potential of desflurane has been demonstrated to be similar to that of isoflurane [20].

Some patients (6–12%) exposed to sevoflurane develop arrhythmias, mostly atrial or junctional [21, 22]. A study performed in infants (mean age 7.5 months) found that sevoflurane induction caused a 20% incidence of junctional bradycardia (less than 80 beats/min). Isoflurane, when utilized in children for electrophysiologic studies and radiofrequency ablation for SVT, does not affect sinoatrial or atrioventricular (AV) node conduction, and all arrhythmias were easily induced [23]. There are case reports of sevoflurane causing torsade de pointes in children with congenital long QT syndrome; this effect may be due to the increase in HR often seen with induction of anesthesia with this agent [24].

In a study of sevoflurane inhalation induction using electronic anesthesia data, Kraemer and colleagues [25] compared 209 children with Down syndrome with or without CHD with 268 healthy controls without Down syndrome or CHD. Fifty-seven percent of the Down syndrome patients experienced age-defined hypotension and bradycardia during the first 6 minutes of anesthesia, as compared with 12% of patients without Down syndrome or CHD (odds ratio, 9.56; 95% confidence interval 6.06–15.09). Bradycardia was not further characterized, i.e., sinus vs. junctional. Nogami and colleagues [26] describe a case of transient cardiac arrest in a 14-year-old Down syndrome patient with repaired ASD, VSD, and PDA during inhalational induction with 5% sevoflurane for a dental procedure. Severe bradycardia (HR <30 bpm) developed 1 minute after induction, followed by asystole. The mechanism for cardiac arrest was postulated to be secondary to autonomic cardiac dysfunction commonly seen in the Down syndrome population.

Few studies to date have addressed the effects of the different anesthetics on an important group of pediatric patients with heart disease: patients with cardiomyopathy or significantly decreased systolic ventricular function. Volatile agents were commonly employed in two retrospective series of anesthesia in children with cardiomyopathy. Lynch and colleagues administered volatile agents in 26% of 236 inductions, and only four patients (1.7%) had cardiac arrest on induction; none of the four received volatile agents [27]. Kipps and colleagues reported a series of 33 children; 12% received volatile agents for induction and 64% received them for maintenance [28]. Although there were 15 patients with severe complications, defined as significant hypotension, arrhythmia, cardiac arrest, extracorporeal membrane oxygenation cannulation, or death, no conclusions could be drawn about any association with use of volatile agents. Rather, severe ventricular dysfunction (shortening fraction <16%) was the most important predictor of complications.

Diastolic function with halothane and isoflurane has been studied in animal models of cardiomyopathy [29, 30]. The two agents differ, with halothane producing negative lusitropic effects, while isoflurane conserves or may even improve diastolic function. There are no reports measuring diastolic function in response to anesthetic agents in patients with CHD.

KEY POINTS: VOLATILE AGENTS

- Depression of myocardial contractility and CO is greatest with halothane, minimal with sevoflurane, and least with isoflurane and desflurane at end-tidal concentrations up to 1.5 MAC.
- All volatile agents may depress myocardial contractility and CO at high doses; infants less than 6 months of age are at the greatest risk.
- Patients with significantly decreased ventricular systolic function are presumed to be at greatest risk for further myocardial depression from any volatile agent.

Nitrous oxide (N_2O)

Despite its ubiquitous use as an adjunct to anesthetic induction and maintenance in patients with CHD, information regarding the effect of N_2O on hemodynamics in patients with CHD is very limited. Its use may be relatively contraindicated where increased FiO_2 is employed, or where enlargement of enclosed air collections is possible, such as in any intracardiac or intrathoracic surgery. Reports of increased pulmonary vascular resistance (PVR), sympathetic stimulation, or significantly decreased CO in response to N_2O in adult patients have not been substantiated in children with or without the cardiac disease [31, 32].

In infants and small children with normal hearts, Murray and colleagues found that addition of 30 and 60% N_2O to 1 MAC halothane or isoflurane resulted in a decreased HR and cardiac index, without changing EF and stroke volume measured echocardiographically [33]. These authors also demonstrated that when 0.6 MAC halothane or isoflurane was substituted for 60% N_2O during 0.9 MAC isoflurane or halothane anesthesia, HR, MAP, and cardiac index were unchanged [34].

In 14 patients with CHD recovering from surgery, Hickey and colleagues [35] administered 50% N_2O and observed a decrease of 9% in HR, 12% in MAP, and 13% in systemic cardiac index. However, mean pulmonary artery pressure and PVR were not significantly changed in these well-ventilated patients with a $PaCO_2$ of 34–35, and pH of 7.47–7.49, even in patients with elevated PVR at baseline. This single report represents the total number of patients with CHD in which N_2O administration has been carefully studied. Despite this paucity of information, extensive clinical experience has demonstrated N_2O to be safe and effective, particularly as an adjunct to inhaled induction of anesthesia for congenital heart surgery.

Opioids and benzodiazepines

Fentanyl and sufentanil have been studied as a sole anesthetic in patients with CHD. Hickey, Hansen, and colleagues [36–38] provided the basis for this technique with a series of studies in neonates and infants less than 1 year of age undergoing complex repairs, ranging from the Norwood operation to complete repair of biventricular lesions. Fentanyl doses of 50–75 μg/kg, and sufentanil doses of 5–40 μg/kg, administered with pancuronium 0.1–0.15 mg/kg, provided excellent hemodynamic stability with minimal changes in HR and blood pressure throughout the surgery. The increase in pulmonary artery pressure and resistance in response to suctioning in infants recovering from cardiac surgery was eliminated with 25 μg/kg fentanyl. Moore and colleagues [39] demonstrated that 5, 10, or 20 μg/kg sufentanil in children aged 4–12 years had no effect on EF as measured by echocardiography in patients undergoing repair of biventricular lesions. Increases in HR, blood pressure, and stress hormones were more effectively blunted by the higher doses. Glenski and colleagues [40] reported M-mode echocardiographic measures of contractility, blood pressure, and HR response using fentanyl (100 μg/kg) or sufentanil (20 μg/kg) in children aged 6 months to 9 years. Measurements were made at three different times: after a premedication with morphine and scopolamine, after induction, and after tracheal intubation. These opioids decreased both EF and shortening fraction after induction, but they returned to or above baseline after intubation.

Midazolam is often added to fentanyl anesthesia to provide sedation and amnesia, as a substitute for low-dose volatile anesthetic agent, particularly in hemodynamically unstable patients and young infants, where the myocardial depressant effects of volatile agents are more pronounced. Fentanyl and midazolam combinations have been studied in two different clinically utilized dose regimens to simulate 1 and 1.5 MAC of volatile agents (fentanyl 8–18 μg bolus followed by 1.7–4.3 μg/kg/h infusion, then repeat bolus at 50% of the original doses followed by increase of infusion by 50%, depending on age; midazolam 0.29 mg/kg bolus followed by 139 μg/kg/h infusion, then repeat bolus 50% of the original dose, followed by increase in infusion of 50% for all ages) for induction and the pre-bypass period in congenital heart surgery in biventricular patients [8] (Figure 10.3). Vecuronium was used for muscle relaxation in order to isolate the effects of the other two agents on hemodynamics. Measurements of CO and contractility were made by echocardiography. Fentanyl/midazolam caused a significant decrease (22%) in CO despite preservation of contractility. This was predominantly due to a decrease in HR. Co-administration of a vagolytic agent such as atropine [41] or pancuronium would probably preserve CO. The added effect of midazolam on echocardiographic indices of contractility has

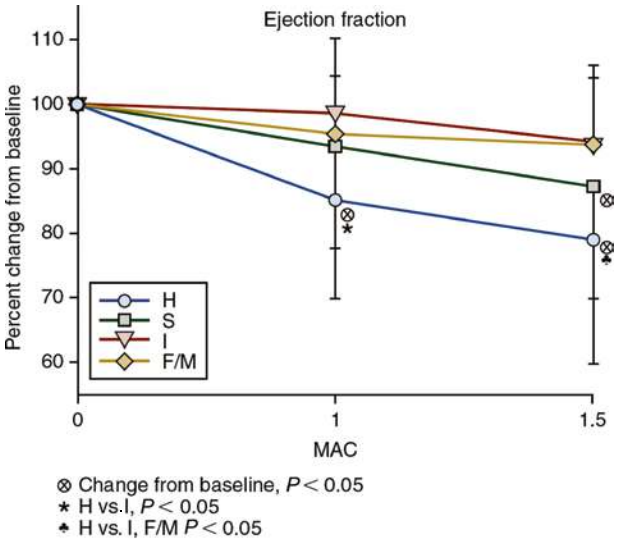


Figure 10.3 Hemodynamic changes assessed by echocardiography in 54 patients with two-ventricle congenital heart disease. (A) Ejection fraction. (B) Cardiac output. H, halothane; F/M, fentanyl/midazolam; I, isoflurane; MAC, minimum alveolar concentration; S, sevoflurane. See text for details. (Source: Rivenes et al. [8]. Reproduced with permission of Wolters Kluwer Health, Inc.)

not been previously reported, however, increased inotropic support requirements have been documented in infants receiving sedation after cardiac surgery with the addition of midazolam bolus totaling 0.3 mg/kg, and infusion of 0.1–0.2 mg/kg/h in the early postoperative period [42].

The stress response to major cardiac surgery in infants and children has been the subject of considerable interest. Anand and Hickey reported the use of high dose sufentanil at a total mean dose of 37 μg/kg as the sole anesthetic for complex neonatal surgery [43]. The sufentanil was continued by infusion for 24 hours postoperatively. This regimen was compared with halothane plus morphine (mean dose of 0.35 mg/kg) intraoperatively, followed by intermittent morphine and diazepam postoperatively. Stress response, as measured by changes in adrenal hormones, cortisol, glucose, and lactate, was significantly reduced in the sufentanil group, and mortality and major complications such as sepsis and necrotizing enterocolitis were also significantly reduced. A later study from the same institution of 45 infants averaging 3 months of age undergoing biventricular repair with deep hypothermic cardiopulmonary bypass has been reported [44]. A total fentanyl dose of 100 μg/kg was administered, given either as intermittent boluses of 25 μg/kg, or as boluses plus infusion, with or without midazolam, and all regimens resulted in a significant endocrine stress response to cardiac surgery. Despite this, the outcome was excellent in all groups, with no adverse outcomes related to the anesthetic technique or the surgical stress response. The sole hemodynamic difference between the regimens was a lower MAP during cooling on bypass in the group who received midazolam. Finally, Duncan and colleagues [45] reported a dose–response study of 2, 25, 50, 100, and 150 μg/kg fentanyl before bypass in 40 children averaging 13 months and 8.5 kg. The 2 μg/kg group had significant increases in pre-bypass norepinephrine, glucose, and cortisol, and significantly higher HR and blood pressure than all other groups. A dose of 25 μg/kg or higher eliminated changes in these parameters for the duration of the surgery. It is difficult to interpret the significance of these stress response studies because they were evaluated by different age groups and lesions. Also, there was more than one decade between reports, during which time there were significant improvements in surgical, bypass, and postoperative management. If any group of patients had benefited from attenuation of the stress response, it would appear to be neonatal patients undergoing complex surgery. Current approaches to early extubation favor lower intraoperative opioid doses, e.g., <10–20 μg/kg fentanyl and use of adjuvants such as dexmedetomidine or regional anesthesia, rather than completely ablating the stress response [46]. Chapter 24 presents an extensive discussion of early extubation approaches for congenital cardiac surgery.

Remifentanil is a synthetic ultra-short-acting narcotic agent metabolized by plasma esterases with a half-life of 3–5 minutes that is independent of the duration of infusion [47]. It is particularly useful for short non-cardiac procedures with intense stimulation where opioid-based anesthesia and its hemodynamic stability would be desirable, yet where rapid emergence is also important. Donmez and colleagues [48] reported a series of 55 children undergoing cardiac catheterization with a remifentanil infusion of 0.1 μg/kg/min. This regimen maintained excellent cardiovascular stability, with minimal changes in HR, blood pressure, or oxygen saturation. Fifty-eight percent of patients required additional sedation with midazolam or ketamine. Apnea was infrequent, and a time to recovery score of 5 (10-point scale) was only 2–4 minutes. Patients undergoing long cardiac catheterization procedures could potentially benefit from this agent.

Remifentanil infusion at 0.3 μg/kg/min increased sinus cycle and Wenckebach cycle length from baseline but did not affect atrial-His or His-ventricular interval, or AV node, atrial, ventricular, or accessory pathway effective refractory period in 14 patients undergoing electrophysiology study and ablation for SVT [49]. In a similar study of 29 patients receiving 0.2 or 0.4 μg/kg/min remifentanil, the larger dose prolonged sinoatrial conduction time and sinus node recovery time, but not atrial-His interval [50]. These electrophysiological effects should be taken into account if the drug is used for electrophysiological studies.

Remifentanil administration has been reported for ASD repair, where patients are extubated in the operating room (OR) [51]. It apparently does not bind to the cardiopulmonary bypass (CPB) circuit [52] and its clearance in children before and after CPB appears to be predictable within a narrow range, making it a potentially useful agent for "fast-track" anesthesia and early extubation for simple surgical procedures. Friesen and colleagues compared remifentanil 0.3–0.7 μg/kg/min with fentanyl 15 μg/kg, both with isoflurane and pancuronium, in fast-track pediatric cardiac operations (ASD and VSD repairs) and found that HR was significantly slower in the OR in the remifentanil group, but there was no difference in time to extubation, analgesic requirements in ICU, nausea/vomiting or hypertension in ICU, or in ICU length of stay [53]. Akpek and colleagues compared higher-dose remifentanil (2 μg/kg load and 2 μg/kg/min maintenance infusion) with fentanyl (20 μg/kg load and 20 μg/kg/h infusion) in 33 infants with pulmonary hypertension undergoing surgery for repair of left-to-right shunting defects. Both groups had a midazolam infusion. There were no clinically important differences in hemodynamic, respiratory, or oxygen saturation parameters between groups, and no difference in clinical outcomes [54]. Thus, despite some theoretical advantages due to its pharmacokinetic profile, there are few clinically significant differences between remifentanil and fentanyl.

KEY POINTS: OPIOIDS AND BENZODIAZEPINES

- Fentanyl, sufentanil, and remifentanil have minimal effect on myocardial function, even at large doses.
- Synthetic opioids decrease catecholamine release and other measures of stress response, including pulmonary hypertension, at moderate and large doses.
- Complete ablation of the stress response with large opioid doses is employed less often in recent years without decrement in outcomes.
- Midazolam (and other benzodiazepines) in large doses may increase inotropic support needs in infants.

Propofol

Propofol has become a popular agent for sedation for cardiac catheterization procedures and induction of general anesthesia for cardiac surgery. In plasma concentrations found in routine clinical use, propofol has minimal negative inotropic effects in isolated animal cardiac preparations [55] or in human adult atrial muscle strips [56].

In children with normal hearts, propofol at induction doses consistently decreases systolic and mean arterial pressure by 5–25% without changing HR [57]. In a case series of 13 preterm neonates of 29–32 weeks gestational age, a propofol bolus of 1 mg/kg decreased MAP from 38 to 24 mmHg, and 5 of 13 patients had a severe decrease to <25 mmHg [58]. There has been one published study using echocardiography to assess myocardial contractility and CO in infants with normal hearts induced with propofol [57]. The shortening fraction or cardiac index was not changed, and SVR decreased by 14 and 27% at 1 and 5 minutes after induction, respectively. Load independent measures of contractility (stress velocity index and stress shortening index) decreased significantly from baseline at 5 minutes after induction with propofol.

Williams and colleagues [59] measured the hemodynamic effects of propofol in 31 patients aged 3 months to 12 years at a dose of 50–200 µg/kg/min undergoing cardiac catheterization (Figure 10.4). They found that propofol significantly decreased MAP and SVR; however, there was no change in systemic CO, HR, mean pulmonary artery pressure, or PVR. In patients with cardiac shunts, the net result was a significant increase in the right-to-left shunt, a decrease in the left-to-right shunt, and decreased Qp : Qs, resulting in a statistically significant decrease in PaO_2 and SaO_2, as well as reversal of the shunt from left-to-right to right-to-left in two patients. In another study of patients undergoing cardiac catheterization, Lebovic and colleagues [60] demonstrated that patients could experience a 20% decrease in HR or MAP. Combining propofol infusion with ketamine infusion for cardiac catheterization procedures demonstrated less change in MAP, preservation of baseline HR, and little effect on recovery time [61].

Propofol has no significant effect on sinoatrial or AV node conduction, or on the ability to induce SVT, and therefore is desirable as a primary agent during electrophysiologic studies and radiofrequency ablation [23, 62]. However, ectopic atrial tachycardia may be suppressed by propofol [63].

Although propofol is very useful for cardiac catheterization, short, stimulating procedures, and possibly for short-term sedation after cardiac surgery, its long-term use as an ICU sedative is contraindicated, with several reports of otherwise unexplained metabolic acidosis and myocardial failure after long-term (>48 hours), high dose use in pediatric patients [64, 65]. The mechanism of this cardiovascular collapse is postulated to be due to disruption of fatty acid oxidation caused by impaired entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain [66]. Although a recent case series of short-term, low- to medium-dose post-anesthetic propofol infusion (median 7 hours) has been described without complication in 12 high-risk CHD patients with pulmonary hypertension, airway malacia, or underlying chromosomal abnormality, this practice should be limited to those centers with substantial expertise and experience with this technique [67]. Propofol infusions of duration greater than 6 hours, as might be observed for long cardiac catheterization procedures, are not recommended because of the potential for the propofol infusion syndrome.

In summary, propofol can be utilized in patients with adequate cardiovascular reserve who can tolerate a mild decrease in contractility and HR, and a decrease in SVR. Propofol may cause an increased intracardiac right-to-left shunt, and reversal of shunt in some patients, (i.e. acyanotic TOF), and thus hemodynamic data obtained in the cardiac catheterization laboratory should be interpreted accordingly. Although propofol use for induction of anesthesia has been described for patients with cardiomyopathies in several case series [27, 28], many authorities recommend against its use, particularly in hypertrophic or dilated cardiomyopathy, where even a small reduction in afterload and preload from propofol's venodilatory properties can result in cardiovascular collapse [68].

KEY POINTS: PROPOFOL

- Propofol at induction doses causes a mild decrease in myocardial contractility, but a significant decrease in MAP and HR, as well as some preload reduction from venodilation.

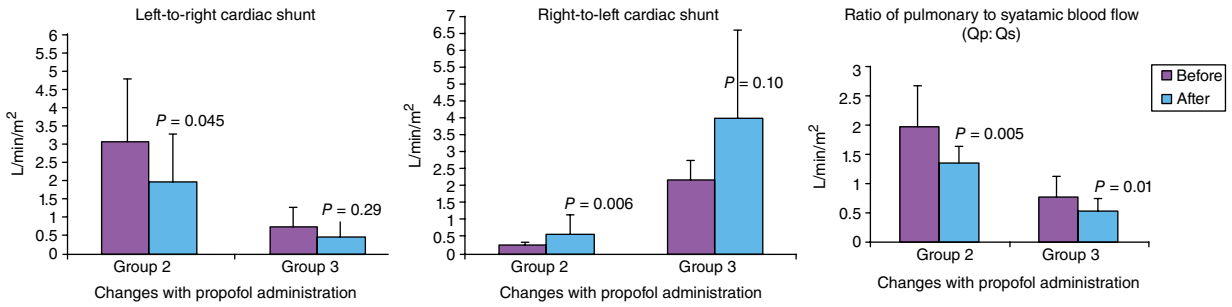


Figure 10.4 Changes in intracardiac shunting in response to propofol induction and infusion in children undergoing cardiac catheterization. Group 2, patients with net left-to-right cardiac shunting; group 3, patients with net right-to-left cardiac shunting. Qp : Qs decreased significantly in both groups. (Source: Williams et al. [59]. Reproduced with permission of Wolters Kluwer Health, Inc.)

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- Propofol infusion has little effect on pulmonary vascular pressure and resistance, but decreases SVR, resulting in an increase in right-to-left shunting.
- Because of its effects to decrease preload, afterload, and myocardial contractility, propofol should be used with great caution, if at all, in patients with significantly decreased ventricular function, and those with left ventricular outflow obstruction.

Ketamine

The general anesthetic and analgesic effects of ketamine are mediated by its interaction with *N*-methyl-D-aspartate receptors in the brain [69]. It increases HR, blood pressure, and CO through central nervous system-mediated sympathomimetic stimulation and inhibition of the reuptake of catecholamines. Ketamine is a direct myocardial depressant when studied in isolated myocyte preparations [70] and in adult human failing atrial and ventricular muscle trabeculae [71] (Figure 10.5). The direct myocardial depression caused by ketamine may be unmasked when administered to patients whose sympathomimetic responses are already maximally stimulated from cardiomyopathy, or another condition leading to poor myocardial reserve, because a further increase in catecholamine release is limited. Similarly, if the patient is chronically receiving ß-adrenergic agonists, catecholamine receptors may be downregulated, resulting in a diminished response to endogenously generated catecholamines, allowing the myocardial depressant effects of ketamine to predominate.

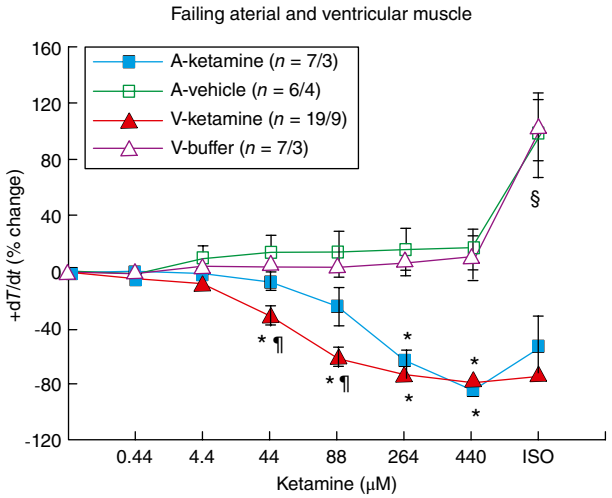


Figure 10.5 Developed tension over time (d*T*/d*t*) in cardiac muscle trabeculae in explanted hearts from adults undergoing cardiac transplantation in response to increasing ketamine concentrations. The upper limit of clinical concentration is 44 μM after a 2 mg/kg induction dose. A, atrial muscle; V, ventricular muscle; vehicle, control solution without ketamine; buffer, Krebs–Henseleit buffer control. $^{*}P < 0.05$ *versus* vehicle control; $P < 0.05$ *versus* A-Ketamine; $^{§}P < 0.05$ *versus* preceding dose. Numbers in parentheses represent numbers of muscle strips/number of patients. ISO, change with addition of 1 μM isoproterenol. (Source: Sprung et al. [71]. Reproduced with permission of Wolters Kluwer Health, Inc.)

The mechanism of myocardial depression is by inhibition of L-type voltage-dependent Ca^{2+} channels in the sarcolemmal membrane. An increased extracellular Ca^{2+} concentration may enhance this effect [70]. This direct myocardial depression effect is greater than that produced by etomidate [56]. In a patient with end-stage cardiomyopathy awaiting heart transplant, hemodynamic collapse occurred after the induction of anesthesia with ketamine [72]. In a study comparing ketamine (1.5 mg/kg) and sufentanil (mean total dose 3.42 μg/kg) for induction of anesthesia in 20 patients with end-stage cardiomyopathy undergoing cardiac transplantation, ketamine was found to increase MAP, SVR, central venous pressure, and pulmonary artery pressure, and decrease stroke volume index significantly [73]. Cardiac index decreased slightly, but not to a statistically significant degree. The sum total of the hemodynamic effects of ketamine induction in these patients was less myocardial work at the expense of a higher myocardial wall tension. Sufentanil induction did not change any of these parameters from baseline.

Other well-recognized untoward effects associated with ketamine use do not differ among patients with CHD. These include emergence reactions, excessive salivation, and an increase in cerebral metabolism, intracranial pressure, cerebral blood flow, and cerebral oxygen consumption [69].

Despite the adverse effects of ketamine, this drug has been a mainstay of induction of general anesthesia in patients with CHD [74, 75]. Administration can be intravenous (IV) or intramuscular (IM), and it will reliably maintain HR, blood pressure, and systemic CO at an induction dose of 1–2 mg/kg IV or 5–10 mg/kg IM, and a maintenance dose of 1–5 mg/kg/hour in patients with a variety of congenital heart diseases, including TOF [76, 77] (Figure 10.6).

Ketamine's effect on pulmonary vascular resistance has been investigated. Morray and colleagues [78] demonstrated that in patients undergoing cardiac catheterization, 2 mg/kg ketamine caused a minimal (<10%) increase in mean pulmonary artery pressure and in the ratio of PVR to SVR (Rp : Rs), with no change in direction of shunting or Qp : Qs. Hickey

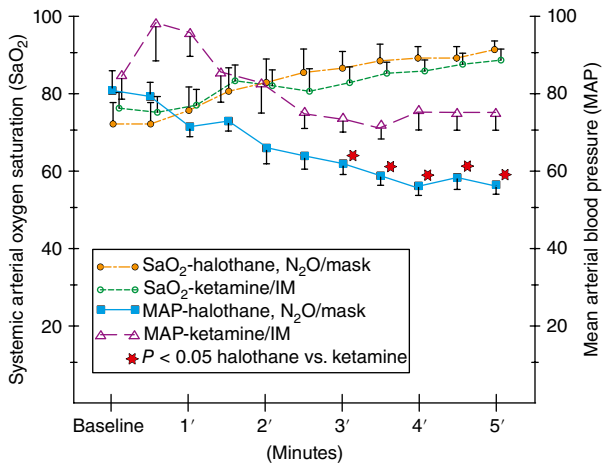


Figure 10.6 Oxygen saturation and mean arterial pressure in response to induction with intramuscular (IM) ketamine vs. halothane in patients with right-to-left cardiac shunting, most of whom had tetralogy of Fallot. (Source: Greeley et al. [76]. Reproduced with permission of Wolters Kluwer Health, Inc.)

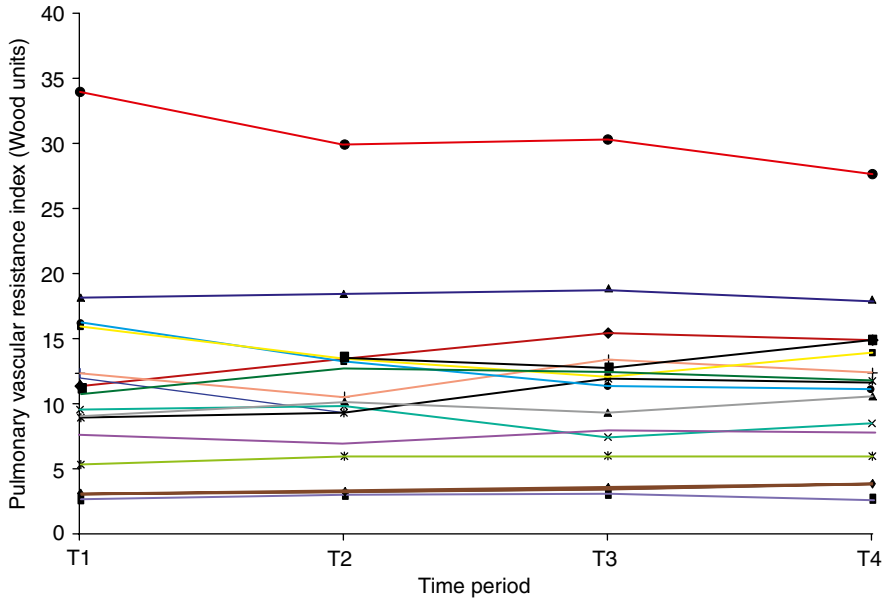


Figure 10.7 Pulmonary vascular resistance changes in 15 children with pulmonary hypertension undergoing cardiac catheterization, in response to ketamine 2 mg/kg intravenously, followed by an infusion of 10 μg/kg/min while breathing spontaneously with a baseline of 0.5 MAC sevoflurane. T1, baseline before ketamine; T2, 5 minutes after ketamine load; T3, 10 minutes after ketamine load; and T4, 15 minutes after ketamine load. (Source: Williams et al. [80]. Reproduced with permission of Wolters Kluwer Health, Inc.)

and colleagues [79] studied 14 postoperative infant cardiac surgery patients who had normal $PaCO_2$, breathing spontaneously through nasotracheal tubes. Ketamine 2 mg/kg had no effect on pulmonary artery pressure or calculated PVR in patients with either normal or elevated baseline PVR. Williams and colleagues reported that ketamine (2 mg/kg load, followed by an infusion of 10 μg/kg/min) did not change PVR at all in 15 children with severe pulmonary hypertension, when breathing spontaneously with a baseline of 0.5 MAC sevoflurane [80] (Figure 10.7). Williams and colleagues also performed a retrospective review of anesthetic technique and outcomes of 92 patients with pulmonary hypertension undergoing 192 anesthetics for noncardiac surgery, catheterization, and other diagnostic procedures, with ketamine administered for either induction or maintenance in 149 procedures (78%) [81]. Pulmonary hypertension was mild in 23%, moderate in 37%, and severe in 40%. There were nine major complications, including three cardiac arrests (1.7% incidence), and 20 minor complications; the majority of minor complications were self-limiting arrhythmias and hypotension. Ketamine administration was not associated with any of these complications, whether administered as the sole anesthetic agent or combined with volatile agents or propofol. Friesen and colleagues [82] administered ketamine (2 mg/kg) to 34 children with known pulmonary hypertension undergoing elective pulmonary hypertension studies with a controlled airway and ventilation. No pulmonary vasodilating medications were used simultaneously. Mean pulmonary artery pressures and PVR were clinically unchanged in this patient cohort. Ketamine appears to be a safe anesthetic option in children with mild to severe pulmonary hypertension.

Ketamine, supplemented with small doses of midazolam and/or morphine, has been used for interventional cardiac catheterization procedures [83] and for postoperative analgesia after cardiac surgery in children. Hemodynamic stability has been excellent, with few complications. The most notable adverse effect was transient apnea in 10% of spontaneously breathing newborns undergoing balloon atrial septostomy in the catheterization laboratory.

There is limited information regarding the effect of ketamine on electrophysiologic study parameters. Char and colleagues reported on 22 children aged 5–17 years undergoing electrophysiologic study and ablation for SVT who had a baseline propofol infusion for sedation [84]. Dexmedetomidine loading dose 1 μg/kg followed by infusion of 0.7 μg/kg/h was initiated, and electrophysiologic parameters measured. Then, with dexmedetomidine still infusing, a ketamine load of 1 mg/kg followed by infusion of 1 mg/kg/h was given, and parameters again measured. Dexmedetomidine depressed sinus node function (sinus node recovery time), prolonged QT interval, and increased AV node refractory period. All of the abnormal parameters were returned completely or partially to baseline values after ketamine. Atiyeh and colleagues reported on a 21-year-old female undergoing electrophysiologic study for refractory paroxysmal idiopathic ventricular tachycardia (VT) [85]. Maintenance anesthesia consisted of low dose propofol, alfentanil, and sevoflurane, and VT could not be induced despite isoproterenol infusion being increased to 5 μg/kg/min. After initiation of ketamine 15 μg/kg/min, VT could be easily and reproducibly induced, allowing successful mapping and ablation of VT focus.

Intramuscular induction of anesthesia may be achieved with ketamine 5 mg/kg, succinylcholine 4 mg/kg, and atropine 20 μg/kg mixed in the same syringe. This regimen is useful for small patients who present to the operating room without IV access in whom the inhalational

induction of anesthesia may produce undesirable hemodynamic effects. Endotracheal intubation can usually be achieved in 3–5 minutes, and attention can be turned to establishing IV access with the airway secure and a stable hemodynamic state. Ketamine may also be employed as a premedication, with an oral dose of 5–6 mg/kg most commonly administered.

In summary, ketamine is an attractive choice for IV or IM induction of anesthesia in patients with CHD with good or moderately limited hemodynamic reserve, including those with pulmonary hypertension or cyanosis. However, care must be taken in patients with severely limited cardiac reserve and depressed myocardial contractility. Such patients may be chronically receiving ß-adrenergic or similar agents, or their own endogenous sympathomimetic system might be maximally stimulated because of a low CO state. The myocardial depressant properties of ketamine may be unmasked, leading to hemodynamic compromise.

KEY POINTS: KETAMINE

- Ketamine will increase HR and blood pressure and preserve or increase myocardial contractility in patients with good hemodynamic reserve.
- Ketamine may act as a direct myocardial depressant in patients with poor ventricular function in whom myocardial β-adrenergic receptors are downregulated from endogenous or exogenous catecholamines.
- Ketamine is a safe anesthetic in pulmonary hypertension if oxygenation and ventilation are maintained.

Etomidate

Etomidate is an imidazole derivative introduced into clinical practice in 1972. It is thought to produce its hypnotic effects (without analgesia) by interaction with gamma-aminobutyric acid receptors [69]. Besides having a desirable lack of effect on hemodynamics, etomidate reduces cerebral blood flow and cerebral metabolic rate of oxygen consumption (30–50%), and intracranial pressure. It has little effect on ventilation, does not release histamine, and does not change airway smooth muscle tone. Of all of the available IV induction agents, etomidate consistently demonstrates the least direct myocardial depression in several *in vitro* models. Two well-designed studies using adult human atrial and ventricular tissue demonstrated no effect of etomidate on myocardial contractility in concentrations seen in clinical use (Figure 10.8). In the same model, ketamine showed slight, and thiopental strong, negative inotropic effects in clinical concentration ranges. This was true even in abnormal myocardial samples of ventricular tissue taken from hearts removed for cardiac transplantation [56, 86]. In a study of right ventricular tissue excised from infants and children during TOF repair, etomidate did not change contractility in the clinical concentration range in an *in vitro* tissue bath study, but did blunt responsiveness to isoproterenol at high concentrations, raising the possibility that the pediatric myocardium may respond differently after etomidate [87].

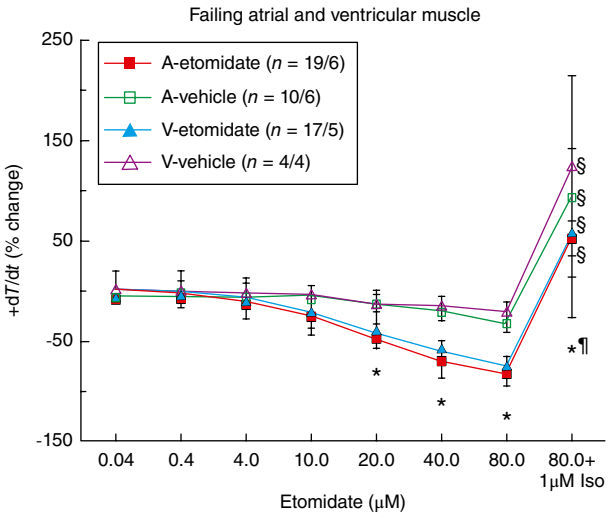


Figure 10.8 Developed tension over time (d*T*/d*t*) in cardiac muscle trabeculae in explanted hearts from adults undergoing cardiac transplantation in response to increasing etomidate concentrations. The upper limit of clinical concentration is 4 μM. A, atrial muscle, V, ventricular muscle; vehicle, 35% propylene glycol, in which etomidate is solubilized. $^{*}P < 0.05$ *versus* A-vehicle control; $^{¶}P < 0.05$ *versus* V-vehicle control, and $^{§}P < 0.05$ *versus* preceding dose. Numbers in parentheses represent numbers of muscle strips/number of patients. Iso, change with addition of 1 μM isoproterenol. (Source: Sprung et al. [86]. Reproduced with permission of Wolters Kluwer Health, Inc.)

These beneficial effects of etomidate are offset by a number of undesirable effects. Etomidate is water-insoluble and is thus formulated in propylene glycol, commonly producing pain on injection, which may be ameliorated by pretreatment with lidocaine and 1 : 1 dilution with sterile water. A new etomidate formulation dissolving the drug in a fat emulsion of medium and long-chain triglycerides virtually eliminates pain on injection in children [88]. Myoclonic movement, hiccoughs, and nausea and vomiting are frequent [69]. It should be noted that, as in adults, a single dose of etomidate used for induction in pediatric patients undergoing cardiac surgery with CPB suppresses the usual increase in plasma cortisol levels by inhibiting 11-ß-hydroxylase, the enzyme that converts 11-deoxycortisol to cortisol [89]. Cortisol levels returned to normal 24 hours later. Two adult studies have reported effects of etomidate induction on 30-day outcomes. Komatsu and colleagues reported on 2,144 ASA III and IV patients given etomidate for induction for non-cardiac surgery, propensity-matched with 5,233 given propofol [90]. Seventy-four percent of patients had cardiovascular disease, and those receiving etomidate had an odds ratio of 2.5 for death and 1.5 for cardiovascular morbidity and a longer hospital stay, but no difference in infectious morbidity or intraoperative vasopressor use. The authors speculate that adrenal suppression could have a bearing on this association. Wagner and colleagues reported a cohort of 3,127 adults undergoing cardiac surgery, 62% of whom received etomidate for induction [91]. No difference in severe hypotension, in-hospital mortality, mechanical ventilation time, or hospital length of stay was demonstrated either before or after propensity score analysis. They conclude that etomidate should remain an acceptable option in these patients.

There are a few published reports of the hemodynamic effects of etomidate in children with CHD. Twenty patients with a variety of congenital defects were studied in the cardiac catheterization laboratory. These authors found that etomidate at 0.3 mg/kg bolus followed by an infusion of 26 μg/kg/min had similar effects as ketamine 4 mg/kg followed by an infusion of 83 μg/kg/min, namely a slight increase in HR but no change in MAP during induction or the 60-minute infusion [92]. Sarkar and colleagues [93] studied etomidate bolus 0.3 mg/kg in 12 children undergoing cardiac catheterization for device closure of ASD, or radiofrequency ablation of atrial arrhythmias. There were no significant changes in any hemodynamic parameter, including HR, MAP, filling pressures, vascular resistances, Qp : Qs, or mixed venous oxygen saturation. Dhawan and colleagues studied 30 children under 12 years old undergoing cardiac catheterization with FiO_2 0.21 and basal sedation with morphine and midazolam, who had direct hemodynamic measurements before and after a 0.3 mg/kg bolus of etomidate [94]. In 15 patients with right-to-left shunt (TOF, VSD/PS, VSD/PA), there was no change in HR, right atrial pressure, MAP, Qp : Qs, or arterial blood gas values. In 15 patients with left-to-right shunts (VSD, ASD, PDA, aortopulmonary window), all of whom had significant baseline pulmonary hypertension, there was also no change in HR, right atrial pressure, mean pulmonary artery pressure (69 mmHg before, 71 mmHg after), Qp : Qs, PVR index (PVRI), or SVR index (SVRI). Dennhardt and colleagues [95] studied 50 neonates and infants (mean age 3.4 months) with congenital heart disease undergoing cardiac surgery, in whom general anesthesia was induced with etomidate. Effects on mean arterial blood pressure, regional cerebral oxygen saturation, and cardiac index were evaluated (Figure 10.9). This patient population exhibited stable systemic and regional cerebral perfusion after a single bolus of 0.4 mg/kg etomidate, leading the authors to conclude that etomidate is a beneficial induction agent in infants with congenital heart disease, or those with expected limited hemodynamic reserve.

A case report of stable hemodynamics in a pediatric patient with end-stage cardiomyopathy receiving a second anesthetic 4 weeks after cardiovascular collapse with ketamine induction (see earlier) demonstrates the utility of etomidate in this population [72]. Etomidate has also been utilized for induction of anesthesia in adults with congenital cardiac conditions such as ruptured aneurysm of the sinus of Valsalva, and cesarean section in a patient with uncorrected coronary artery to pulmonary artery fistula and was demonstrated to be devoid of cardiovascular effects in these patients [96, 97].

It would appear that etomidate is best utilized in patients with the most limited cardiac reserve. It seems to be particularly useful in teenagers or adults with poorly compensated palliated CHD presenting for cardiac transplantation, or revision of previous surgeries. Adrenal suppression occurs with even a single dose of etomidate, and consideration should be given to administer additional supplemental corticosteroids in patients receiving corticosteroids, or at risk of prolonged adrenal suppression. Many patients receiving etomidate for induction will already be receiving corticosteroids as part of their regimen for transplant or cardiac surgery. Repeated or prolonged administration of etomidate is not recommended for this reason.

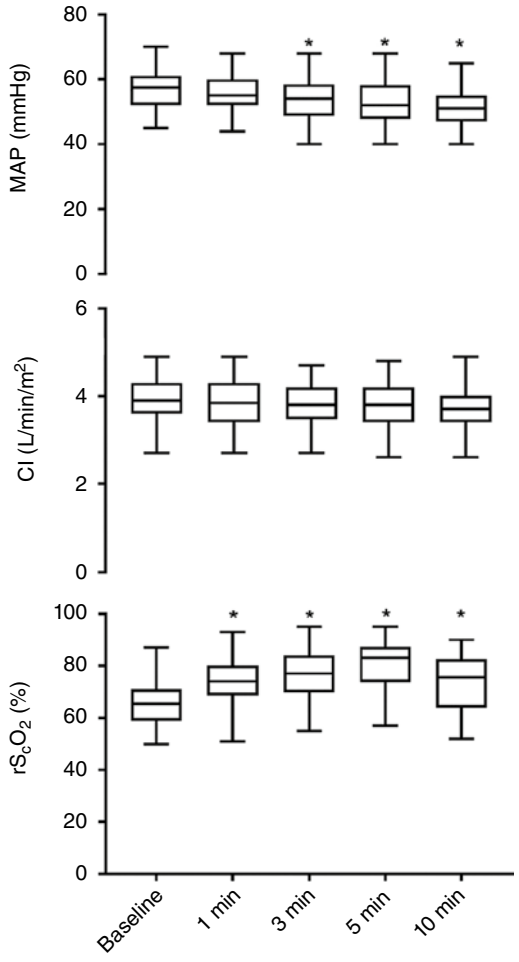


Figure 10.9 Mean arterial blood pressure, cardiac index and regional cerebral oxygen saturation at baseline and 1, 3, 5, and 10 minutes after induction with 0.4 mg/kg etomidate in neonates and infants undergoing cardiac surgery. (Source: Dennhardt et al. [95] / John Wiley & Sons / CC BY 4.0.)

KEY POINTS: ETOMIDATE

- Etomidate has no direct myocardial depressant effect at clinically administered doses, and as such is a preferred induction agent for patients with poor ventricular function.
- Etomidate has no effect on systemic or pulmonary hemodynamics when administered to patients with intracardiac shunting, including those with pulmonary hypertension.
- Etomidate will suppress adrenal function with a single induction dose.

Dexmedetomidine

Dexmedetomidine was introduced in the US in 1999 as a sedative agent for mechanically ventilated adults in intensive care settings. It is an IV agent that is an imidazole

derivative, and a highly selective α_2-adrenergic receptor agonist (1620 : 1 α_2–α_1 activity, vs. 220 : 1 for clonidine). Dexmedetomidine is a centrally acting agent with α_2-receptor binding sites in the locus ceruleus in the brain, producing sedation, and α_2 receptors in the spinal cord, producing some analgesic effect. Dexmedetomidine loading doses, particularly large doses of 0.75–1 µg/kg administered rapidly over <10 minutes, may cause systemic hypertension with binding to peripheral arterial α_2 receptors [98]. With a continuous infusion, dexmedetomidine causes a dose-dependent decrease in HR and MAP by decreasing CNS sympathetic nervous system activity. It also potentiates opioid effects and is thus potentially suitable for use both during and after pediatric cardiac surgery, as a component of a general anesthetic and as a sedative/analgesic agent in the intensive care unit (ICU). The usual dose for sedation is 0.2–0.7 µg/kg/hour; a loading dose of 0.5–1 µg/kg given over 10 minutes can be utilized if desired. It has minimal effect on respiration, and its clearance of 13 mL/kg/min, volume of distribution of 1.0 L/kg, and terminal half-life of 1.8 hours in children without heart disease are similar to adult values [99]. In infants aged 1–24 months receiving dexmedetomidine sedation after congenital heart surgery with bypass, clearance using allometric scaling was 28 mL/kg/min$^{0.75}$, and central volume of distribution was 1.2 L/kg [100]. In both premature infants and full-term neonates <30 days of age undergoing congenital heart surgery, dexmedetomidine clearance is substantially reduced and elimination half-life is substantially increased to as high as 7.6 hours for preterms. Both values assume near-adult levels after about 44 weeks postconceptional age [101, 102].

Because it is an imidazole derivative structurally similar to etomidate, dexmedetomidine theoretically has the potential for adrenal suppression with prolonged use. In 99 pediatric patients undergoing VSD repair, ASD/VSD repair, or Tetralogy of Fallot repair, plasma cortisol concentrations were compared after administration of dexmedetomidine (loading dose of 0.5 µg/kg, followed by infusion of 0.5 µg/kg/hour), etomidate (bolus dose of 0.3 mg/kg), or a control anesthetic. The cortisol level was found to decrease in all patients after induction of anesthesia, and return to baseline within 24 hours, but the degree of decrease at three hours post-induction was more significant in the group that received etomidate, compared to the control, or the group that received dexmedetomidine (Figure 10.10). Any inhibitory function of dexmedetomidine on the adrenal cortex was of weaker efficacy than that of etomidate [103]. Venn and colleagues reported no difference in cortisol, adrenocorticotropic hormone (ACTH), growth hormone, prolactin, insulin, glucose, and interleukin-6 in 20 adult ICU patients randomized to receive propofol or dexmedetomidine [104]. There were also no differences between the groups in response to ACTH stimulation test. However, Tucker and colleagues described a 1-year-old 10 kg burn patient who received high-dose dexmedetomidine infusion for 7 days and developed hypotension with low baseline cortisol levels and inadequate response to ACTH stimulation test, indicating adrenal insufficiency, which they believed was possibly related to dexmedetomidine [105]. No additional published reports exist implicating dexmedetomidine in adrenal suppression.

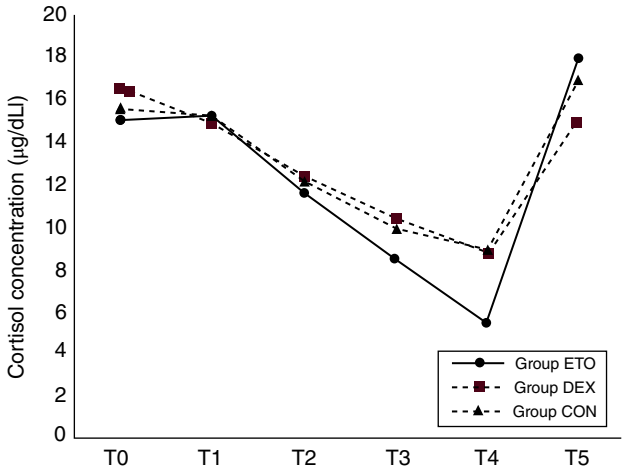


Figure 10.10 Comparison of plasma cortisol concentrations in children with CHD who received etomidate (ETO), dexmedetomidine (DEX) or a control anesthetic (CON). T0, time of intravenous access; T1, immediately after induction; T2, 30 minutes after intubation; T3, after superior and inferior vena cava catheterization; T4, 3 hours after induction; and T5, 24 hours after induction. (Source: Gu et al. [103].)

Dexmedetomidine has been studied as an adjunct agent in general anesthesia for pediatric cardiac surgery. In a study by Muktar and colleagues, dexmedetomidine 0.5 µg/kg load followed by 0.5 µg/kg/h infusion, with an isoflurane–fentanyl–midazolam anesthetic, significantly reduced HR, MAP, cortisol, blood glucose, and serum catecholamine response in children aged 1–6 years undergoing cardiac surgery with CPB, when compared with the baseline anesthetic [106].

Dexmedetomidine has been studied for postoperative sedation after pediatric cardiac surgery. Chrysostomou and colleagues studied 38 pediatric patients of median age 8 years after two-ventricle repair with CPB. Thirty-three of 38 patients had tracheal extubation in the OR. Dexmedetomidine infusion rate varied from 0.1 to 0.75 µg/kg/h (mean 0.3), and the desired sedation was achieved in 93% of patients, and analgesia in 83% of patients. There was no respiratory depression, but hypotension was observed in 15% of patients [107]. Dexmedetomidine has also been described as useful in weaning opioid-tolerant cardiac surgery patients relatively quickly with no hemodynamic side effects [108].

Dexmedetomidine as a sole sedative agent for pediatric cardiac catheterization was studied by Munro and colleagues in 20 children [109]. A loading dose of 1 µg/kg was followed by an infusion of 1 µg/kg/h, and propofol boluses were given for movement or increasing bispectral index value. Sixty percent of patients required propofol boluses. There was a slight decrease in MAP but not in HR, and no patient experienced airway obstruction or respiratory depression. Dexmedetomidine plus ketamine has been compared with dexmedetomidine plus propofol for pediatric cardiac catheterization in 44 patients [110]. There was no difference in sedation scores or respiratory parameters: HR was slower in the dexmedetomidine group, while MAP was not different. Recovery time was significantly longer in the dexmedetomidine group than in the propofol group.

Table 10.2 Electrophysiologic variables at baseline and after a 20-minute infusion of dexmedetomidine

	Baseline	DEX	*P*
Surface ECG intervals			
SCL	606 ± 140 ms	788 ± 165 ms	<0.01
PR	144 ± 19 ms	162 ± 17 ms	<0.01
QRS	76 ± 11 ms	79 ± 13 ms	NS
QTc	394 ± 9 ms	424 ± 9 ms	<0.01
Sinus automaticity			
CSNRT	212 ± 179 ms	293 ± 180 ms	<0.01
Atrial muscle properties			
AERP	207 ± 31 ms	208 ± 17 ms	NS
AV nodal properties			
AH interval	73 ± 14 ms	82 ± 12 ms	<0.01
AVNBCL	352 ± 87 ms	436 ± 105 ms	<0.01
AVNERP	310 ± 85 ms	360 ± 88 ms	<0.02
VABCL	372 ± 111 ms	460 ± 134 ms	<0.01
His Purkinje properties			
HV interval	40 ± 7 ms	40 ± 6 ms	NS
Ventricular muscle properties			
VERP	220 ± 22 ms	230 ± 19 ms	0.06

Source: Hammer et al. [111]. Reproduced with permission of Wolters Kluwer Health, Inc.

ECG, electrocardiogram; SCL, sinus cycle length; PR, PR interval; QRS, QRS duration; QTC, corrected QT interval; CSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period; AH interval, atrial–His interval; AVNBCL, AV node block cycle length; AVNERP, AV node effective refractory period; VABCL, ventriculoatrial block cycle length; HV interval, His–ventricular interval; VERP, ventricular effective refractory period.

It is important to note that dexmedetomidine frequently causes bradycardia and thus may not be suitable as a sedative for electrophysiologic studies. In 12 children undergoing electrophysiologic studies, Hammer and colleagues found that dexmedetomidine 1 μg/kg load followed by 0.7 μg/kg/h infusion for 20 minutes decreased HR by 15–20%, but more importantly depressed sinus node recovery times, sinus node automaticity, and increased AV nodal block cycle lengths and PR interval [111] (Table 10.2).

In more recent studies, case series reporting dexmedetomidine administration for intraoperative and postoperative use have been described in a variety of congenital and acquired heart diseases, including those with critical heart disease and decreased ventricular function. Klamt and colleagues prospectively randomized 32 children undergoing two-ventricle cardiac repairs to a midazolam–fentanyl anesthetic or a dexmedetomidine–fentanyl anesthetic [112]. Dexmedetomidine was infused at 1.0 μg/kg/h without loading dose for the first hour, and then decreased to 0.5 μg/kg/h, and HR and BP were recorded. Isoflurane was used to supplement the anesthetic and to control hemodynamic variables. HR and BP decreased from baseline in both groups but increased after skin incision only in the midazolam–fentanyl group. Eighty-six percent of the midazolam–fentanyl group required supplemental isoflurane, as compared with 31% of the dexmedetomidine–fentanyl group. In the dexmedetomidine group, two patients required phenylephrine before bypass for hypotension and one required atropine for bradycardia.

In a retrospective review, Lam and colleagues described 50 neonates and infants ≤12 months receiving dexmedetomidine sedation for a median of 78 hours, at doses ranging from 0.1 to 1.5 μg/kg/hour after congenital heart surgery or cardiac transplantation [113]. Despite a significant decrease in HR and MAP as well as central venous pressure after initiation of the dexmedetomidine infusion, inotrope score progressively decreased, and no critical hemodynamic events or bradyarrhythmias were observed that required boluses of IV fluids, adrenergic agents or atropine, or escalation of inotropic support. The authors concluded that dexmedetomidine is safe from a hemodynamic standpoint and can reduce opioid and benzodiazepine dosing. Lam and colleagues also described dexmedetomidine use in 21 infants (median age 3–4.2 months and weight 4.7–6.6 kg) with congestive heart failure as part of a sedation regimen for intensive care and compared safety and efficacy with 23 patients with congestive heart failure who were sedated without dexmedetomidine [114]. All patients were awaiting orthotopic heart transplantation and were studied in the 18 days before transplant; 75% had dilated cardiomyopathy and all but one was receiving mechanical ventilation. Mean arterial pressures were lower in the first 24 hours in the dexmedetomidine group, and HR was lower in the dexmedetomidine group in the first 6 hours. Three patients in the dexmedetomidine group (14%) had greater than a 50% decrease in MAP in the first 3 hours after initiation of dexmedetomidine infusion at 0.5–0.6 μg/kg/hour; one of the three also had bradycardia to 48 beats/min. Opioid and benzodiazepine doses were significantly lower in children receiving dexmedetomidine. The authors concluded that dexmedetomidine administration in infants with heart failure appears to be generally safe, but should be used cautiously.

Su and colleagues studied dose–response of dexmedetomidine as a primary sedative in a dose-escalation study of 36 infants aged 1–24 months after cardiac surgery, with loading dose and infusion rates spanning the range of doses used clinically [115]. Heart rates for the entire group decreased from a mean of 161 beats/min at baseline to a mean of 132 beats/min during dexmedetomidine infusion ($P < 0.0001$). The decrease in HR was dose- and plasma level-dependent with larger decreases in higher-dose groups. MAP and inotrope infusion scores did not change significantly during infusion. A single patient in the intermediate dosing cohort experienced intermittent complete heart block 5 hours after dexmedetomidine infusion initiation, resulting in bradycardia, which did not recur following discontinuation. A more recent study by this same group extended the study population to include 23 neonates with CHD after cardiac surgery [116]. Three neonatal patients developed bradyarrhythmias, one developed junctional rhythm, and one developed atrial ectopy. All patients required discontinuation of the dexmedetomidine infusion. One neonatal patient developed hemodynamically significant atrial ectopy, requiring CPR and extracorporeal membrane oxygenation. Their data suggests the need for dexmedetomidine dose reduction in neonates due to decreased clearance, with the greatest reduction required in the first 2 weeks of life.

Dexmedetomidine is often cited as facilitating early tracheal extubation because of its minimal effects on respiration and ability to reduce opioid doses. Le and colleagues

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reported a retrospective review of 269 patients undergoing cardiac surgery, 89 of whom received dexmedetomidine for postoperative sedation, and 180 matched controls from the year before introduction of dexmedetomidine to their institution [117]. There were no differences in any ventilation parameter: 42% of both groups had tracheal extubation in the OR; 75% of controls and 76% of dexmedetomidine patients were extubated in the first 24 hours, and the mean ventilator time was 29 hours in the control group and 35 hours in the dexmedetomidine group ($P = 0.17$), with no differences in patients <12 months. The authors concluded that dexmedetomidine did not have a significant impact on early extubation.

The effect of dexmedetomidine on pulmonary artery pressure and resistance has been reported in several studies. Lazol and colleagues studied 22 patients (median age 11 months) after reparative two-ventricle cardiac surgery, who received a dexmedetomidine loading dose (median 0.62 μg/kg) and infusion (median 0.5–0.65 μg/kg/h) and had echocardiographic estimation of pulmonary artery pressure using tricuspid regurgitation jet velocity [118]. Median pulmonary artery systolic pressure decreased from 30 mmHg before dexmedetomidine to 24 mmHg at 6 minutes after the loading dose, and 26 mmHg at 1 hour ($P < 0.001$). The ratio of pulmonary to systemic systolic pressure decreased from 33 to 25% ($P = 0.002$). There were no changes in inotropic infusions or left ventricular contractility. Friesen and colleagues studied 42 patients undergoing cardiac catheterization: 21 for routine post-transplant surveillance, and 21 for pulmonary hypertension studies [119]. After sevoflurane induction, endotracheal anesthesia was maintained with midazolam and remifentanil, and the response to dexmedetomidine loading doses of 0.5, 0.75, or 1.0 μg/kg over 10 minutes was measured. Most hemodynamic responses were similar in both groups, with a significant decrease in HR and an increase in SVRI. Cardiac index did not change. There was a small, statistically significant increase in pulmonary artery pressure in transplant patients, but not in those with pulmonary hypertension. Changes in PVRI and PVRI/SVRI were not significant in either group. Kanchi and colleagues [120] studied 25 children with known pulmonary hypertension undergoing elective cardiac catheterization/intervention with monitored anesthesia care. After sedation with midazolam and ketamine boluses, a bolus dose of 1 μg/kg dexmedetomidine was given over 10 minutes, followed by an infusion at 0.3 μg/kg/h until the end of the procedure. No significant change in mean pulmonary artery pressures was measured throughout the catheterizations. The authors concluded that dexmedetomidine can be used safely in patients with PAH undergoing cardiac catheterizations with the use of spontaneous ventilation.

Dexmedetomidine has been demonstrated in several case series to decrease the incidence of postoperative ventricular and supraventricular tachydysrhythmias in infants and children after congenital heart surgery with bypass [121]. The use of prophylactic dexmedetomidine to prevent postoperative junctional ectopic tachycardia in children after repair of congenital heart diseases has been described. In a prospective randomized study, El Amrousy and colleagues [122] studied 90 children with CHD undergoing cardiac surgery. 60 patients received dexmedetomidine (0.5 μg/kg loading dose completed 10 minutes prior to induction, with 0.5 μg/kg/h infusion continued for 48 hours postoperatively), and 30 patients received saline placebo. The incidence of JET was significantly reduced in the dexmedetomidine group (16.7% in placebo group vs. 3.3% in dexmedetomidine group; $P = 0.02$). Gautam and colleagues [123] studied 134 pediatric patients undergoing surgeries involving closure of a VSD (TOF repair, VSD patch closure, AVSD repair). 99 patients were exposed to dexmedetomidine either intraoperatively prior to incision, intraoperatively after weaning from bypass, or on arrival to the ICU. After multivariate analysis, the intraoperative pre-CPB initiation of dexmedetomidine was significantly associated with a greater reduction in JET (odds ratio 0.04; $P = 0.006$), compared to intraoperative post-CPB initiation (odds ratio 0.16; $P = 0.024$) and postoperative initiation (odds ratio 0.50; $P = 0.365$).

Dexmedetomidine is a potentially useful agent as an adjunct to general anesthesia, a postoperative sedative, and an adjunct sedative for cardiac catheterization (non-electrophysiologic studies) in pediatric patients with CHD. The patient must be able to tolerate the predictable decrease in HR, and frequent decrease in MAP associated with dexmedetomidine infusion. Clearance of dexmedetomidine is reduced in neonates, necessitating lower doses in this age group and heightened monitoring for side-effects.

KEY POINTS: DEXMEDETOMIDINE

- Dexmedetomidine allows for reduction of doses of opioids and benzodiazepines and may be a useful adjunct to intraoperative general anesthesia, and as a component of postoperative sedation regimens.
- Dexmedetomidine boluses in larger doses result in hypertension; side-effects of infusions include hypotension and bradycardia.
- Dexmedetomidine affects cardiac conduction and may suppress supraventricular and ventricular arrhythmias, but sinus and junctional bradycardia and sinus arrest are unusual but potentially serious side-effects.

The major hemodynamic and cardiac rhythm effects of the anesthetics, sedatives, and analgesics discussed in preceding sections are presented in Table 10.3.

Neuromuscular blocking agents and antagonists

Succinylcholine

Succinylcholine is rarely indicated for anesthesia for CHD because of its association with the development of malignant hyperthermia, hyperkalemic cardiac arrest, and bradycardia after IV bolus administration. Succinylcholine will produce a more rapid onset of muscle relaxation than non-depolarizing muscle relaxants [124] and generally its use is limited to full-stomach emergency indications, i.e., cardiac transplant, treatment of laryngospasm, and as a component of an intramuscular induction.

Table 10.3 Major hemodynamic and cardiac conduction effects of anesthetic, analgesic, and sedative agents

Drug class	Drug	Cardiovascular effects						Comments
		Heart rate	Cardiac rhythm	MAP/SVR	PAP/PVR	Myocardial contractility	Cardiac output	
Volatile anesthetics	Halothane	– – –	Ventricular extrasystoles, sinus/junctional bradycardia	– – –	– –	– – –	– – –	Contraindicated with decreased ventricular function
	Sevoflurane	–/+	Junctional bradycardia	–/NC	–	–	–/NC	
	Isoflurane	++	NC	– –	–	–/NC	NC	Preserves myocardial contractility to 1.5 MAC in CHD
	Desflurane	+++	NC/sinus tachycardia	–	–	–/NC	NC	
Nitrous oxide	Nitrous oxide	–	NC	–	NC	NC	–	
Benzodiazepines	Midazolam	–/NC	NC	–	NC	–/NC	–/NC	
Synthetic opioids	Fentanyl, sufentanil, remifentanil	– –	Sinus bradycardia	–/NC	– –	NC	–/NC	Preferred for prevention/treatment of pulmonary hypertension
Alkylphenol derivative	Propofol	–	Sinus bradycardia	– – –	NC	–	– –	Decreases preload; avoid in preload/afterload dependent patients
Imidazole derivative	Etomidate	NC	NC	NC	NC	NC	NC	Adrenal suppression
Arylcyclohexylamine	Ketamine	+++	NC/sinus tachycardia	++	NC	NC/–	+/–	Direct myocardial depressant in heart failure
α_2 agonist, imidazole derivative	Dexmedetomidine	– – –	Sinus/junctional bradycardia, heart block, asystole	++ with bolus; – – – with infusion	++ with bolus; – – – with infusion	NC	NC/–	Delayed clearance and longer half-life in neonates; bradyarrhythmias are a major adverse effect

α_2, alpha-2-adrenergic receptor; CHD, congenital heart disease; MAC, minimum alveolar concentration; MAP, mean arterial pressure; NC, no change; PAP, pulmonary artery pressure; SVR, systemic vascular resistance; +, small increase; ++, moderate increase; +++, large increase; –, small decrease; – –, moderate decrease; – – –, large decrease.

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Infants and children frequently exhibit bradycardia, junctional rhythm, ventricular premature beats and, rarely, asystole, after IV dosing of succinylcholine 1–2 mg/kg without atropine pretreatment. The frequency of these arrhythmias increases with a second dose. A dose of 4 mg/kg given IM, either alone, or with atropine 20 μg/kg and ketamine 5–10 mg/kg in the same syringe rarely causes bradycardia [125].

Pancuronium

Pancuronium is used in doses of 0.1–0.3 mg/kg for initial relaxation [126] and is particularly desirable in many small infants and young children with CHD because of the vagolytic and mild sympathomimetic effects, which preserve or increase HR, especially in the face of concomitant bradycardia from high-dose opioid anesthesia. In recent years, this drug has become unavailable in many parts of the world.

Vecuronium

Vecuronium is devoid of cardiovascular effects in children [127]. It is a useful agent when increases in HR are undesirable (e.g. in hypertrophic cardiomyopathy). When no uncertainties about the ability to manage the airway are evident, it is a useful alternative to succinylcholine in a dose of 0.3–0.4 mg/kg for modified rapid sequence induction.

Rocuronium

Rocuronium is a moderately rapid-onset, intermediate-duration, non-depolarizing neuromuscular blocker that is useful at a dose of 0.6–1.2 mg/kg IV. At the upper dose ranges it is an acceptable substitute for succinylcholine for modified rapid sequence induction. Cardiovascular effects are minimal, but because it causes pain on injection, or because it is a weak vagolytic medication, an increase in HR is often observed after injection. This agent may be utilized for IM administration in doses of 1.8–2 mg/kg, and when injected into the deltoid muscle will produce suitable intubating conditions in 3–4 minutes [128].

Atracurium and cisatracurium

Atracurium and cisatracurium are non-organ-dependent for elimination and are attractive choices in the face of significant hepatic and renal dysfunction. Atracurium at high dosages frequently causes histamine release, resulting in hypotension when injected rapidly [124], making it undesirable for many patients with CHD. Cisatracurium is a stereoisomer of atracurium, also degraded by Hoffmann elimination, does not release histamine, and like vecuronium is devoid of cardiovascular effects, even when administered rapidly [129].

Antagonists

The muscarinic effects of neostigmine must be blocked by atropine or glycopyrrolate to prevent potentially serious decreases in HR. Because the onset of cardiovascular effects of neostigmine and glycopyrrolate are similar, a useful regimen is to utilize neostigmine and glycopyrrolate in the same syringe in a 5 : 1 ratio of neostigmine: glycopyrrolate (i.e., 75 : 15 μg/kg) injected slowly to minimize the small risk of arrhythmia with neostigmine. Despite longstanding use of neostigmine for reversal of neuromuscular blockade, it may cause bradycardia or cardiac arrest, even if administered with appropriate anticholinergic agents. Sawasdiwipachai and colleagues reported on a case of a 1–year-old who suffered a cardiac arrest 2 weeks after a heart transplant, after a myocardial biopsy, and reversal of cisatracurium neuromuscular blockade with 70 μg/kg neostigmine and glycopyrrolate 14 μg/kg [130]. Acute cardiac rejection and an abnormal conduction system were postulated as causes in this infant, with direct effect on the muscarinic receptors playing a role. Two additional cases of cardiac arrest in children with transplanted hearts have also been reported [131]. The authors suggest preadministration of glycopyrrolate to avoid effects related to the muscarinic receptor, and consideration of sugammadex as an alternative with no effect on acetylcholine receptors, as reversal strategies in patients with transplanted hearts.

Sugammadex is a synthetic modified γ-cyclodextrin used for reversal of steroidal neuromuscular blockade. It forms tight 1 : 1 water-soluble complexes with free steroidal neuromuscular blocking drug, leading to rapid removal of the drug from the plasma. The effect of the neuromuscular blockade is terminated by rapid diffusion of the drug away from the neuromuscular junction, rather than competitive inhibition at the acetylcholine receptor. Thus, sugammadex is devoid of muscarinic effects [132]. It was approved for use in adults in 2015, and its use is steadily increasing in the pediatric population.

Sugammadex has been reported to prolong QTc interval in some adult patients [133]. De Kam and colleagues administered sugammadex to 80 healthy adult volunteers in a randomized, double-blind, placebo-controlled study designed to assess its effect on QTc intervals [134]. Sugammadex doses up to 32 mg/kg were studied, with either rocuronium 1.2 mg/kg or vecuronium 0.1 mg/kg, and an active control drug known to prolong QTc intervals. No effect was detected on the QTc intervals up to 24 hours after administration of sugammadex. Cammu and colleagues studied 12 adult patients with heart failure and EF < 25% undergoing general anesthesia with rocuronium neuromuscular blockade, and reversal with sugammadex 2 mg/kg [135]. Blood pressure and HR did not change for the first 10 minutes after administration, and both had increased by 30 minutes. Reversal of neuromuscular blockade was effective in all patients but, at 2.8 minutes, the mean time to reversal was longer than observed in healthy patients. No sugammadex-related adverse events were reported.

Recent studies have investigated the hemodynamic effects of sugammadex in pediatric patients. In a prospective randomized clinical study, Li and colleagues [136] compared the use of sugammadex (4 mg/kg) and neostigmine (30 μg/kg) with atropine (15 μg/kg) for reversal of neuromuscular blockade in 60 children aged 1–6 years old undergoing ASD or VSD repairs. Patients administered sugammadex had a significantly higher heart rate after drug administration (103 vs. 97 bpm; $P = 0.03$). The mean arterial pressure after drug administration was found to be similar in both groups. The authors conclude that sugammadex demonstrates superiority in maintenance of heart rate in children undergoing cardiac surgery. Alsuhebani and colleagues [137] studied the incidence of bradycardia (HR below fifth percentile for age) after sugammadex administration in 221 children (median age 8 years; median weight 28 kg). The median sugammadex dose

was 2 mg/kg (range 2–15.7 mg/kg). Bradycardia was seen in 18 patients (8%) at a median of 2 minutes after sugammadex administration, with no association between the dose administered and the incidence of bradycardia. Notably, 38% of the patients who developed bradycardia had comorbid cardiac conditions, with multivariate logistic regression showing that bradycardia risk after sugammadex administration was increased for patients with cardiac comorbidities (odds ratio 3.8; $P = 0.015$). However, no instances of bradycardia in this patient cohort were hemodynamically significant, and no treatment or intervention was necessary. These authors conclude that the use of sugammadex is safe in pediatric patients. To date, no physiologic mechanism has been described for the development of bradycardia in association with the administration of sugammadex.

KEY POINTS: NEUROMUSCULAR BLOCKING AGENTS AND ANTAGONISTS

- Succinylcholine may cause bradycardia, junctional rhythm, ventricular premature beats, and asystole in patients with CHD.
- Vecuronium, rocuronium, and cisatracurium are generally devoid of cardiovascular effects.
- Neostigmine may cause bradycardia or sinus arrest; adequate doses of anticholinergic agents must be administered concomitantly.
- Sugammadex is a novel reversal agent for neuromuscular blockade with a mechanism of action that avoids muscarinic side effects.

Special conditions affecting anesthetic pharmacokinetics and pharmacodynamics in congenital cardiac anesthesia

Intracardiac shunts

The presence of a right-to-left intracardiac shunt decreases the rate of rise of the concentration of inhaled anesthetic in the arterial blood, as a portion of the systemic CO bypasses the lungs and then dilutes the anesthetic concentration in the systemic arterial blood [138]. The anesthetic concentration in the blood thus never equals the exhaled concentration. Huntington and colleagues [138] studied six children with right-to-left shunts from a fenestrated Fontan operation whose average pulmonary to systemic blood flow ratio was 0.58. These patients achieved an arterial anesthetic concentration (Fa) of only 55% of inspired halothane concentration (Fi) after 15 minutes during wash-in of 0.8% halothane. After closure of the right-to-left shunt (occlusion of Fontan fenestration in the cardiac catheterization laboratory), the arterial concentration of halothane was equal to the inspired concentration. This difference between Fa and Fi is greater during induction or washout, and greater with less soluble drugs, such as sevoflurane, desflurane, and N_2O, than with more soluble drugs, such as halothane. Conversely, if the blood concentration of a volatile agent is high, the rate of decrease during washout is slowed with right-to-left shunting. This is an important consideration if myocardial depression occurs. The usual approach to reduce or discontinue the volatile agent and increase minute ventilation is often ineffective in this situation.

Other studies have demonstrated a delay in inhalational induction time in patients with right-to-left intracardiac shunting. Zeyneloglu and colleagues [139] investigated the induction characteristics of sevoflurane in 62 children undergoing open-heart surgery. Thirty-two patients had acyanotic heart disease, and 30 patients had cyanotic heart disease with right-to-left intracardiac shunting on preoperative cardiac catheterization. The duration to loss of eyelash reflex was found to be longer in the cyanotic group, as compared to the acyanotic group (56 vs. 45 seconds, $P = 0.044$). Similarly, Hasija and colleagues [140] studied 93 pediatric patients undergoing elective cardiac or noncardiac surgery under general anesthesia induced with sevoflurane. The time to induction (determined by loss of eyelash reflex and BIS <60) was significantly longer in the cyanotic children with right-to-left shunt undergoing cardiac surgery, with an almost two times delay, compared to the time to induction for patients with acyanotic CHD, or without CHD.

In the face of significant right-to-left intracardiac shunting, IV agents given by bolus may pass directly into the left side of the heart with less dilution by systemic venous blood and passage through the pulmonary vascular system. This may result in transiently high arterial, brain, and cardiac concentrations of drugs such as lidocaine [141]. Intravenous induction agents and muscle relaxants may also achieve sufficient arterial and brain concentrations more rapidly with right-to-left intracardiac shunts [142].

Left-to-right intracardiac shunts have little effect on the speed of induction with inhaled anesthetic agents [143]. The recirculation of blood through the lungs results in increased uptake of anesthetic and in a higher blood anesthetic concentration in the pulmonary capillaries, which reduces the concentration gradient between the alveoli and the pulmonary capillary blood, reducing anesthetic uptake. The two effects cancel each other. Only in the case of severe congestive heart failure from left-to-right shunt, with significant interstitial and alveolar edema, would left-to-right intracardiac shunting be expected to slow inhalation induction from the combined effects of diffusion limitation and ventilation–perfusion mismatch, resulting in alveolar dead-space ventilation in which no new anesthetic agent is taken up.

Cardiopulmonary bypass

The onset of CPB affects plasma levels of IV drugs by a number of different mechanisms [144]. Hemodilution of the patient's blood volume by a factor of 50–300%, depending on the size of the patient and the priming volume of the circuit, causes an immediate reduction in plasma levels. Many drugs also bind to the membrane oxygenator and other components of the bypass circuit, resulting in a further decrease in plasma levels. This effect is variable and is dependent on the drug, its size and lipid solubility (octanol: water partition coefficient), the type of bypass circuit used (i.e. silicone vs. polypropylene), the age and size of the patient, and the

plasma and bypass prime albumin concentrations. Hypothermia slows the metabolism of all drugs by reducing the rate of reaction of all enzymes involved in drug metabolism, whether they are in the liver (cytochrome P450 system), kidney, or plasma. Rewarming significantly increases the rate of metabolism of IV agents.

A constant, stable plasma fentanyl level [145] can be achieved in most children through the administration of a loading dose of 30–50 μg/kg followed by an infusion of 0.15–0.3 μg/kg/min. Plasma fentanyl levels decrease by 70–75% immediately upon institution of CPB with a silicone membrane oxygenator, presumably due to binding of the drug to oxygenator and bypass tubing. After cooling to 18–25 °C, fentanyl metabolism decreases considerably and free drug concentrations change very little, even without added drug [146]. Metabolism then increases and drug levels decline in the plasma as rewarming proceeds. Data concerning common anesthetic adjuvants such as midazolam suggest similar changes in plasma concentrations [144]. Thus, without supplementation of IV agents such as fentanyl and midazolam, either just before or at the initiation of bypass, plasma levels of IV anesthetics will decline significantly and there is an increased risk of inadequate anesthesia. A similar risk would appear to be true during the final phases of the rewarming period. Indeed, this concept is borne out by studies using bispectral index as an indicator of depth of sedation in children undergoing bypass with mild hypothermia [147]. Modified ultrafiltration has been reported to double the plasma fentanyl concentrations in a study of five neonates and infants, from 12.4 to 27.5 ng/mL, presumably due to hemoconcentration [148].

Volatile agents may be used during bypass to supplement anesthetic depth, or as vasodilators. Isoflurane is most commonly utilized at a concentration of 0.5–2% inspired into the sweep gas of the bypass circuit. Multiple adult studies have demonstrated the effectiveness and relatively rapid wash-in of this agent [144]. The blood levels of isoflurane are highly dependent on the type of oxygenator used. Wiesenack and colleagues reported on isoflurane blood and oxygenator concentrations in 24 adults undergoing elective coronary bypass surgery [149] (Figure 10.11). Isoflurane (1%) was added to the CPB sweep gas, at 3 L/min flows for 15 minutes, and isoflurane concentrations were measured in the blood, and at the oxygenator gas outflow port. Microporous polypropylene (PPL) hollow-fiber membrane oxygenators were compared with plasma-tight poly-(4-methyl-1-pentene) (PMP) membrane oxygenators, and dramatic differences were found. The PPL oxygenator had an area under the curve of blood level of isoflurane 8.5- to 13-fold higher than PMP oxygenators, with almost no blood transfer of isoflurane with PMP models. Isoflurane concentration was also significantly lower at the oxygenator exhaust port with the PMP models, reaching only 60% of inspired levels at 15 minutes, whereas with the PPL models exhaled isoflurane was equal to inspired after less than 5 minutes.

Most CPB oxygenators in clinical pediatric use are PPL models. Pediatric *in vitro* or *in vivo* data have not been published, and because sweep gas flow rates are often less than 1 L/min in small infants, volatile anesthetic uptake is probably much slower. It cannot be assumed that the desired blood anesthetic level is rapidly reached when volatile anesthetic agents are administered through the bypass circuit to infants and small children. In this study, blood levels were continuing to increase after 15 minutes. Washout of volatile agents is also slower at low sweep gas rates, and volatile agents should be discontinued early during the rewarming period to avoid the potential myocardial depressant effects of these agents while attempting to wean the patient from bypass.

Dexmedetomidine use during CPB in pediatric cardiac surgery has been increasing. In a recent phase 1 multicenter study, Zuppa and colleagues [150] investigated the safety and pharmacokinetic properties of dexmedetomidine in 122 neonates and infants aged 0–180 days undergoing repair of ventricular septal defects, D-transposition of the great arteries, or tetralogy of Fallot. Dexmedetomidine clearance during CPB was reduced by 95%, and clearance in the immediate postoperative period was reduced by 50%. Neonates achieved 90% of maximum clearance by 18 days, consistent with other published studies. There were five safety events occurring in the infant cohort: two episodes of junctional rhythm, two episodes of second- or third-degree heart block, and one episode of hypotension. The arrhythmias required temporary atrial or atrioventricular pacing for 30 minutes up to 48 hours. These authors introduce an externally validated pharmacokinetic model in order to achieve low, medium and high steady-state plasma dexmedetomidine concentrations on CPB (Figure 10.12). Using this group's data, Hammer and Shafer [151] constructed an accessible simulation program with dexmedetomidine dosing guidelines during CPB (https://steveshafer.shinyapps.io/stanpumpR_HelpPage/, under "Dexmedetomidine BJA 2020"). With carefully designed dosing strategies, dexmedetomidine is a safe addition to the anesthetic regimen for neonates and infants undergoing cardiac surgery with CPB.

Neuromuscular blocking agents have an enhanced effect during hypothermic bypass, [144] both from decreased metabolism and clearance, and because of the effects of hypothermia to potentiate the pharmacodynamic effects of the drugs at the neuromuscular junction. These effects rapidly reverse themselves during rewarming. These drugs have a small volume of distribution and thus few tissue stores from which to re-equilibrate plasma levels. Thus, plasma levels would be expected to decline in proportion to the hemodilution factor of the pump prime, subject to changes in protein binding. This may be offset by reductions in the patient's plasma volume on bypass due to vasoconstriction. The action of these drugs in response to bypass is accordingly more variable than other commonly used IV anesthetic agents. There is limited pediatric information available. Monitoring of neuromuscular blockade with a twitch monitor is recommended if early reversal is desired.

Hypothermia

Studies performed on animal models reveal hypothermia reduces the MAC of volatile anesthetics [152]. Liu and colleagues [153] studied the MAC of isoflurane in 33 children with left-to-right intracardiac shunts at 37, 34, or 31 °C. They found that MAC was reduced by 28% at 31 °C when compared with normothermia, indicating a decrease in MAC of approximately 5%/°C cooling. The bispectral index value correlates strongly with temperature during mild hypothermic

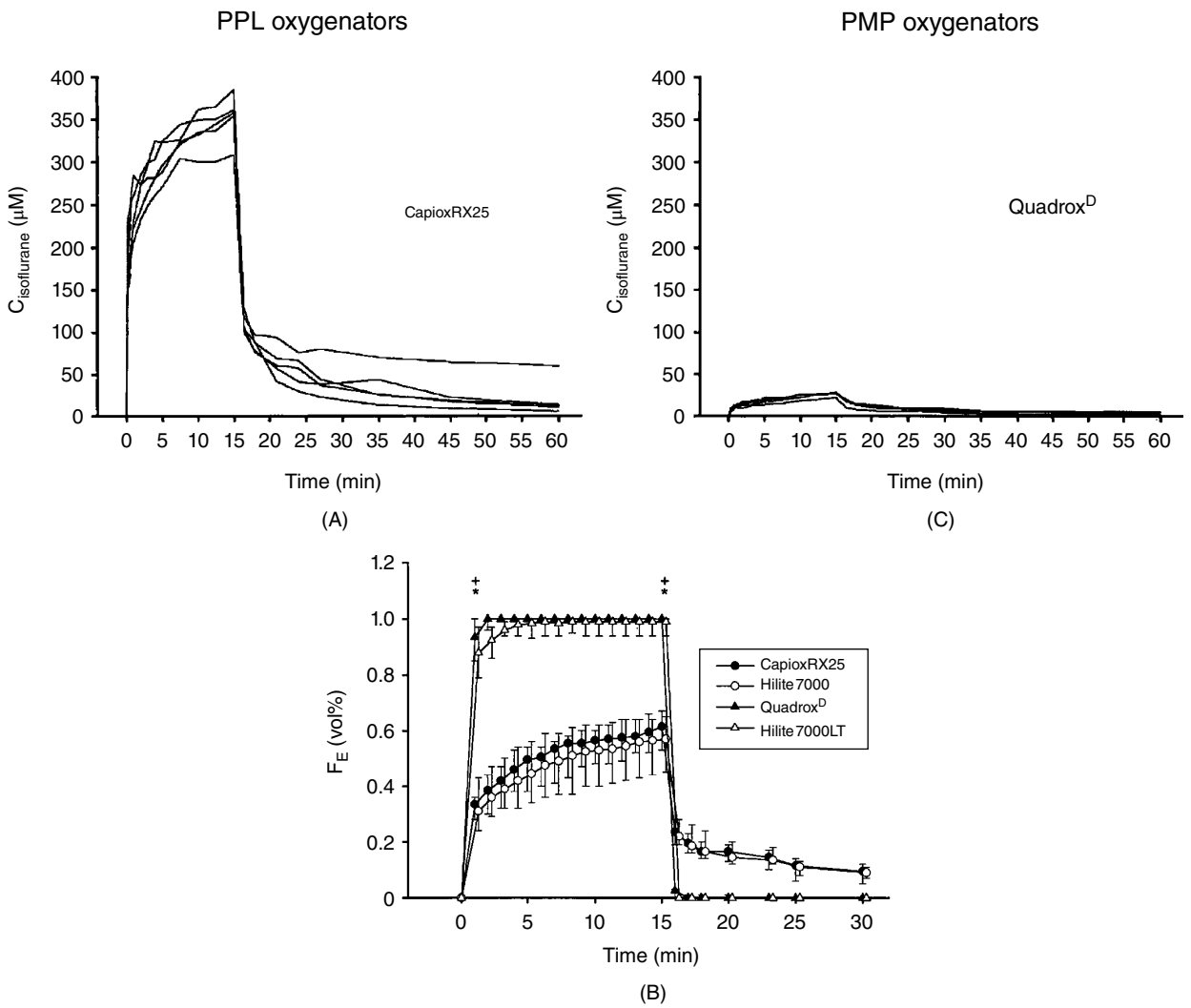


Figure 10.11 Isoflurane blood concentrations ($C_{isoflurane}$ [μM]) for the uptake and elimination sequence for two different oxygenators; each line represents a single patient. (A) CapioxRX25 PPL oxygenator. (B) Oxygenator exhaust port isoflurane (F_E) for uptake and elimination sequence for the four oxygenators. (C) Quadrox D PMP oxygenator. Values are median (range). *, $P < 0.01$ vs. Quadrox D; ⁺, $P < 0.01$ vs. Hilite 7000LT®. Polypropylene (PPL) oxygenators (CapioxRX25, Hilite 7000) had greater transfer of isoflurane across membrane oxygenator and into blood than polymethylpentane (PMP) oxygenators (Quadrox D, Hilite 7000LT). (Source: Wiesenack et al. [149]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Age group (days)	Target Css (pg/mL)	Initial loading dose (μg/kg)	Infusion 1: pre-CPB, first 60 min of CPB (μg/kg/hour)	Loading dose to CPB prime volume (μg/mL)	Infusion 2: after 60 min of CPB ubtil end of CPB (μg/kg/hour)	Infusion 3: 60 min after CPB (μg/kg/hour)
Neonatal (0–21)	200	0.24	0.22	0.004	0.04	0.14
Neonatal (0–21)	500	0.6	0.55	0.01	0.1	0.35
Neonatal (0–21)	700	0.84	0.77	0.014	0.14	0.49
Neonatal (0–21)	1000	1.2	1.1	0.02	0.2	0.7
Infant (22–180)	200	0.29	0.26	0.005	0.05	0.17
Infant (22–180)	500	0.72	0.66	0.012	0.12	0.42
Infant (22–180)	700	1.01	0.92	0.017	0.17	0.59
Infant (22–180)	1000	1.44	1.32	0.024	0.24	0.84

Figure 10.12 Dosing recommendations for targeted dexmedetomidine steady-state concentrations in neonatal and infant cardiac surgery. CPB, cardio-pulmonary bypass; Css, steady-state concentration. (Source: Zuppa et al. [150]. Reproduced with permission of Elsevier)

bypass in children [154], offering supporting evidence that hypothermia alone provides general anesthesia.

KEY POINTS: SPECIAL CONDITIONS AFFECTING ANESTHETICS

- Right-to-left intracardiac shunting slows volatile anesthetic uptake and washout; the greatest effect is in less soluble agents such as sevoflurane and desflurane, while the effect is smaller with the more soluble agents, such as halothane.
- CPB has highly variable effects on anesthetic drug pharmacokinetics and pharmacodynamics, depending on the type of oxygenator, flows, temperatures, and ultrafiltration.
- Hypothermia significantly decreases anesthetic requirements by lowering MAC and slowing metabolism of IV drugs.

Selection of anesthetic regimen in CHD

Pediatric patients with congenital and acquired heart disease are known to be at significantly higher risk for cardiac arrest and death, and other major complications of anesthesia. The four highest risk groups appear to be patients with supra-systemic pulmonary hypertension, severe left ventricular outflow tract obstruction, severe ventricular dysfunction, and infants with single ventricle physiology prior to cavopulmonary anastomosis [9, 27, 28, 155–160]. The incidence of cardiac arrest related to anesthesia is reported to be 0.7–6% in these patient groups, and anesthetic agent selection plays a role in at least some of these adverse outcomes.

The ideal anesthetic regimen for CHD would be devoid of any undesirable hemodynamic effects, would produce analgesia, amnesia, and muscle relaxation, and would be rapidly titratable. Hemodynamic perturbations would be controlled with vasoactive and inotropic agents alone, also rapidly titratable, achieving a desirable separation of anesthetic and hemodynamic effects for the two classes of drugs. The ideal regimen does not exist, and the pediatric cardiac anesthesiologist is left with devising an individualized strategy for each patient, accounting for pathophysiology and desired hemodynamic goals in each patient. Hemodynamic effects are continuously monitored, doses of different drugs are often titrated independently and at frequent intervals, and the anesthesiologist must sometimes change strategies. Vasoactive and inotropic agents must sometimes be added to counteract the untoward effects of a chosen anesthetic regimen.

The ideal anesthetic plan would involve thorough review of all data, including echocardiography and other imaging, careful examination of the patient, and the construction of a set of hemodynamic goals, which also consider the duration and invasiveness of the planned surgery, intervention, or diagnostic study. The well-known difficulties in approaching infants and young children with stranger anxiety and without IV access must frequently be taken into account. Then, an intelligent anesthetic regimen is selected which is likely to achieve the desired goals based on the known cardiovascular effects of the drugs as presented in this chapter. For example, the patient with severe left ventricular outflow tract obstruction has a stroke volume that depends on maintaining adequate preload and afterload. Important hemodynamic goals include avoiding tachycardia and increases in myocardial contractility, and regimens that include large doses of propofol or volatile agents are contraindicated. Patients with dilated cardiomyopathy and decreased ventricular function similarly should not receive agents in doses that further depress myocardial contractility or significantly alter preload or afterload. Patients with significant pulmonary hypertension should have a regimen that avoids large increases in catecholamine secretion from noxious stimuli that could precipitate a pulmonary hypertensive crisis. Chapter 21 discusses hemodynamic management, and Chapters 26–32 present the pathophysiology and anesthetic considerations for each of the major congenital cardiac lesions in detail.

A single-center retrospective chart review of choice of induction techniques for general anesthesia in children with CHD undergoing non-cardiac procedures showed that children of American Society of Anesthesiologists (ASA) three physical status and above and those with CHD of greater severity (based on residual lesion burden and functional status) tend to be induced with etomidate, ketamine, and opioids [161]. However, to date, there have been few, if any, controlled studies of anesthetic regimens and cardiovascular outcomes in CHD. No agent or regimen is proscribed for any particular cardiac lesion, and there are many different approaches for each lesion among experienced pediatric cardiovascular anesthesiologists. Careful consideration of the cardiovascular effects of the drugs and the patient's pathophysiology and desired hemodynamic goals should allow the pediatric cardiac anesthesiologist to devise a safe and effective anesthetic plan for patients with CHD.

KEY POINTS: ANESTHETIC REGIMEN SELECTION

- Review all data carefully and construct a set of desired hemodynamic goals for each patient considering their unique pathophysiology.
- Design an anesthetic drug strategy that is likely to achieve the optimal hemodynamic state.
- Carefully monitor and titrate anesthetic drugs and prepare to change strategies if hemodynamic goals are not achieved.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

8 Rivenes SM, Lewin MB, Stayer SA, et al. Cardiovascular effects of sevoflurane, isoflurane, halothane, and fentanyl-midazolam in children with congenital heart disease: an echocardiographic study of

myocardial contractility and hemodynamics. Anesthesiology 2001;94:223–9. A comprehensive echocardiographic study of the effects of major anesthetic drugs in two-ventricle congenital heart disease. Isoflurane and sevoflurane preserve cardiac output at 1.5 MAC.

13 Ikemba CM, Su JT, Stayer SA, et al. Myocardial performance index with sevoflurane-pancuronium versus fentanyl-midazolam-pancuronium in infants with a functional single ventricle. Anesthesiology 2004;101:1298–305. An echocardiographic study in single-ventricle index demonstrating that sevoflurane and fentanyl/midazolam preserve baseline ventricular function at 1.5 MAC or equivalent.

55 Williams GD, Jones TK, Hanson KA, Morray JP. The hemodynamic effects of propofol in children with congenital heart disease. Anesth Analg 1999;89:1411–6. A classical paper demonstrating the effects of propofol to lower SVR, preserve PVR, increase intracardiac right-to-left shunting and decrease systemic oxygen saturation in patients with right-to-left shunts.

64 Ing RJ, Ames WA, Chambers NA. Paediatric cardiomyopathy and anaesthesia. Br J Anaesth 2012;108:4–12. An excellent review article discussing etiology of cardiomyopathies, and anesthetic drug considerations in major categories of cardiomyopathies.

75 Williams GD, Philip BM, Chu LF, et al. Ketamine does not increase pulmonary vascular resistance in children with pulmonary hypertension undergoing sevoflurane anesthesia and spontaneous ventilation. Anesth Analg 2007;105:1578–84. A carefully performed study in the cardiac catheterization laboratory demonstrating pulmonary hemodynamic change with ketamine, demonstrating no increase in pulmonary artery pressures or resistance with adequate ventilation and oxygenation.

83 Dhawan N, Chauhan S, Kothari SS, et al. Hemodynamic responses to etomidate in pediatric patients with congenital cardiac shunt lesions. J Cardiothorac Vasc Anesth 2010;24:802–7. A recent study in the cardiac catheterization laboratory documenting the lack of systemic and pulmonary hemodynamic change after induction doses of etomidate in 30 children with left to right shunts and pulmonary hypertension, as well as patients with right to left shunts.

100 Su F, Nicolson SC, Zuppa AF. A dose-response study of dexmedetomidine administered as the primary sedative in infants following open heart surgery. Pediatr Crit Care Med 2013;14:499–507. A comprehensive prospective study documenting hemodynamic changes and safety of dexmedetomidine. Heart rate decreased, blood pressure was stable, and a single patient of the 36 studied had transient heart block attributed to dexmedetomidine.

105 Huntington JH, Malviya S, Voepel-Lewis T, et al. The effect of a right-to-left intracardiac shunt on the rate of rise of arterial and end-tidal halothane in children. Anesth Analg; 1999;88:759–62. The classical paper documenting the theory that a right-to-left intracardiac shunt slows the rate of rise of arterial volatile anesthetic agent concentration.

114 Wiesenack C, Wiesner G, Keyl C, et al. in vivo uptake and elimination of isoflurane by different membrane oxygenators during cardiopulmonary bypass. Anesthesiology 2002;97:133–8. A comprehensive study documenting the pharmacokinetic behavior of isoflurane with cardiopulmonary bypass, and the critical importance of the details of the design of the oxygenator which affect this behavior.

116 Liu M, Hu X, Liu J. The effect of hypothermia on isoflurane MAC in children. Anesthesiology 2001;94:429–32. A now classical study documenting the effect of hypothermia on isoflurane MAC in children undergoing cardiopulmonary bypass, documenting an approximately 5% decrease in MAC for every degree centigrade below 37°C.

150 Zuppa AF, Nicolson SC, Wilder NS, et al. Results of a phase 1 multicentre investigation of dexmedetomidine bolus and infusion in corrective infant cardiac surgery. Br J Anaesth 2019;123:839–82. A landmark phase 1 multicentre study establishing the safety and pharmacokinetic properties of dexmedetomidine in neonates and infants undergoing corrective cardiac surgery with cardiopulmonary bypass, highlighting the need for a careful dosing strategy in this patient population due to decreased clearance while on CPB and in the immediate postoperative period.

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CHAPTER 11
Cardiopulmonary Bypass

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Introduction

On May 6, 1953, John H. Gibbon, Jr. successfully performed, for the first time, open-heart surgery using cardiopulmonary bypass (CPB) for the closure of a large atrial septal defect. The heart-lung machine, consisting of a simple oxygenator in conjunction with roller pumps, took over the function of the heart and lungs for a duration of 26 minutes. The machine worked properly during the total bypass time of 45 minutes, apart from some fibrin formation on the oxygenator due to inadequate anticoagulation [1]. Gibbon's success stood at the end of approximately 20 years of developing a heart-lung machine. In a 1937 publication, Gibbon published his first results of an experimental CPB in cats. In 1939, the former president of the American Association of Thoracic Surgeons, Leo Eloesser, said during a discussion following a lecture by Gibbon that his presentation reminded him of the seemingly impossible, fantastic stories of the novel writer, Jules Verne, that later often became reality [2]. In a series of 19 consecutive bypass uses in dogs, 12 of the animals survived. But the idea of perfusion with artificially produced circulating arterial blood did not originate with Gibbon. The idea was first documented in 1812, inspired by the French physiologist, César Julien-Jean Le Gallois. In his monograph "Expériences sur le principe de la vie" he described experiments to define the relationship of the respiratory and nervous system, and blood circulation. On August 9, 1951, in Turin, Dogliotti and Constantini used a partial bypass on humans for the first time [3]. When a patient whose condition during the surgical removal of a large mediastinal tumor drastically deteriorated, a heart-lung machine was used to maintain perfusion for 20 minutes and the patient was stabilized. On March 16, 1943, Willem Johan Kolff observed, during the clinical use of an artificial dialyzer, that oxygen was quickly absorbed by a cellulose membrane. This observation was the basis for the development of membrane oxygenators. Later Kolff presented the design of the first membrane oxygenator at the first Congress of the American Society for Artificial Internal Organs on June 5, 1955 [4]. Also in the 1950s, Arthur Keats, Denton Cooley and colleagues at Texas Children's Hospital pioneered several important breakthroughs in congenital cardiac surgery with bypass, including, in 1959, the first description of heparin–protamine titration [5]. In a seminal 1958 article, they described anesthetic problems in their first 200 cases of congenital heart surgery with bypass, which included

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bypass times; changes in blood gases, electrolytes, and lactate; cardiac rhythm disturbances; and blood transfusions [6]. The first commercial oxygenators became available in the 1960s and the number of open cardiac surgery procedures increased rapidly at that point. Subsequent attempts to use the heart-lung machine to help correct complex congenital heart defects in small infants were hindered by high morbidity and mortality rates until Barratt-Boyes and Castaneda started using deep hypothermic circulatory arrest in the late 1960s and early 1970s. Less than two decades later, pediatric cardiac surgery and anesthesia had progressed to providing multistage palliation for infants with single-ventricle physiology. Today CPB is a standard feature of daily pediatric cardiac anesthesia practice. Advances in neonatal CPB techniques over the last 60 years have been among the most important factors leading to improved outcomes in pediatric cardiac surgery. Extracorporeal perfusion in newborns, infants, and children is in many aspects different from the adult patient. This is caused by the underlying physiologic changes as well as the different pathophysiology secondary to shunt physiology.

In this chapter, we review the equipment and techniques used in CPB, with a primary focus on neonatal and pediatric bypass. We will also summarize the effects of CPB on different organ systems. Extensive reviews on the multiorgan effects of congenital cardiac surgery are presented in Chapter 12, and neurological monitoring and outcomes in Chapter 14. In this chapter, we emphasize specific management issues that occur in daily practice. Further details on specific technical issues can be found in excellent extensive textbooks on the topic [7].

Basic bypass circuit setup

A basic bypass circuit (Figure 11.1) consists of a venous reservoir, an oxygenator/heat exchanger unit, roller pumps for perfusion, suction, and cardioplegia and the connecting

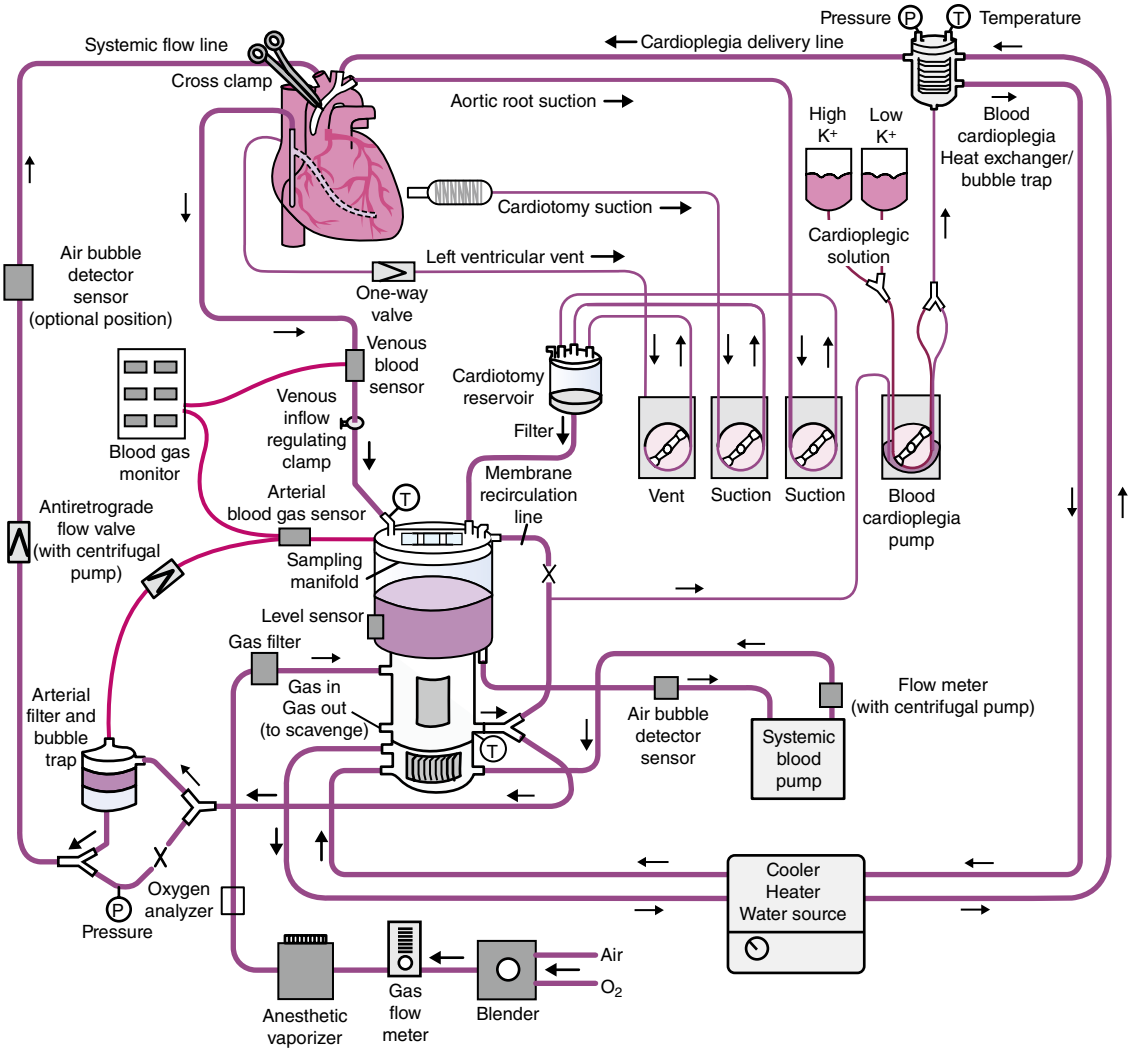


Figure 11.1 Schematic diagram of a cardiopulmonary bypass circuit. This scheme depicts a membrane oxygenator with an integral hard-shell venous reservoir and an external cardiotomy reservoir. Many circuits have the cardiotomy reservoir, venous reservoir, and oxygenator integrated into one single unit. The systemic blood pump may be either a roller or centrifugal pump. Most pediatric venous cannulations are bicaval with two separate venous cannulas instead of the single venous cannula depicted here. Carbon dioxide can also be added to the inspired gas to facilitate pH-stat blood gas management. Arrows indicate the direction of flow; P, pressure sensor; T, temperature sensors; X, placement of tubing clamps. (Source: Hessel et al. [7]. Reproduced with permission of Wolters Kluwer.)

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Table 11.1 Differences between adult and pediatric cardiopulmonary bypass

Parameter	Adult	Pediatrics
Temperature	Rarely below 32 °C	Commonly 18–20 °C
Deep hypothermic circulatory arrest (DHCA)	Rare	Common for arch repair (HLHS, IAA)
Pump prime	Crystalloids	Blood components and albumin
Dilution	25–33%	Up to 200%
Perfusion pressure	50–80 mmHg	30–50 mmHg
Flow rates	2.5 L/min/m^2 or 50–65 mL/kg/min	0–250 mL/kg/min
pH management	Alpha-stat	pH-stat
Hypoglycemia	Rare, only in hepatic injury	Common due to low hepatic glycogen stores
Hyperglycemia	Frequent increases mortality	Less common, may be protective
Cannulation techniques	Standardized, mostly ascending aorta and single-stage venous cannula	Variable, including ductus, aorta, main pulmonary artery; mostly bicaval venous cannulation
Ultrafiltration	Rare	Standard modified ultrafiltration or conventional ultrafiltration

HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch.

tubing, cannulae, as well as monitoring and alarm devices. There are major differences between adult and pediatric CPB, stemming from anatomic, metabolic, and physiologic differences in these two groups of patients (Table 11.1). Much progress has been made in the miniaturization of circuits and components. Current technology allows a total priming volume as low as 95 mL for a neonatal circuit setup allowing transfusion-free repairs in smaller patients down to the 5–10 kg range in some institutions [8–10].

Cannulation and tubing

The selection of cannulas occurs on the basis of flow requirements and anatomic relations. Single-stage venous cannulation is rare and selective superior and inferior vena cava cannulation plus additional cannulation of a left persistent superior vena cava are routine. Thus, the infant patient routinely has an aortic cannula and two venous cannulas. A second aortic cannula may be used for cases of interrupted aortic arch to perfuse the descending aorta (Figure 11.2). Particular care must be observed during inferior vena cava (IVC) cannulation, as obstruction or malposition into a hepatic vein can occur. The addition of a small cannula for venting the systemic ventricle places significant demand on the surgeon to manage the position of the multiple cannulae in the small pericardial space of neonates and young infants. Venting the heart through an existing patent foramen ovale or atrial septal defect (ASD) or creating a small atrial communication is the preferred method for many congenital

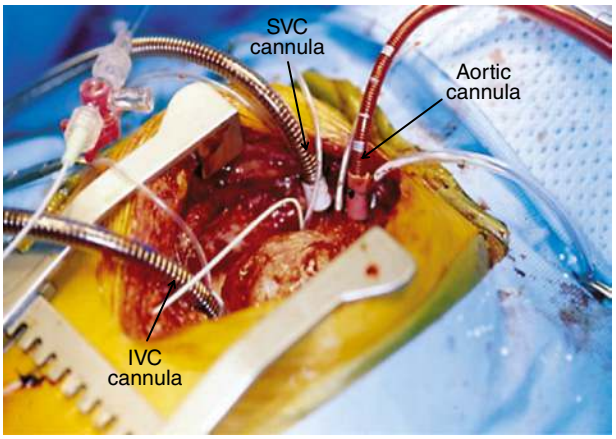


Figure 11.2 Aortobicaval cannulation in a neonate. IVC, inferior vena cava; SVC, superior vena cava.

cardiac surgeons, instead of a cannula in a superior pulmonary vein, to avoid damage to these delicate structures.

In daily clinical practice, the amount of systemic venous return on CPB is directly correlated with the amount of pump flow and vice versa. Venous drainage is often limited by the small size of the cannula and tubing as well as individual characteristics, the circuit used, and the use of accessory systems. Generally, venous drainage is obtained by gravity, placing the venous reservoir of the CPB circuit about 30 cm lower than the level of the heart; in this way, a negative pressure equivalent to about 20–25 mmHg is obtained. This is adequate for the vast majority of adult patients undergoing conventional procedures. In pediatric patients, however, where relatively small-size cannulas and tubing of the venous circuit are used to reduce the pump-priming volume, vacuum-assisted venous return is most often used. In this system, a constant vacuum (up to 80 mmHg) is created in the airtight venous reservoir, allowing more blood to be drained from the patient via the venous line. This system allows the performance of surgical procedures on CPB, even in small infants, without the need for large-size venous tubing and, therefore, without increasing the volume of the pump priming [11, 12]. The major potential limit in the clinical application of this system is the risk of generating gaseous microemboli in the venous circuit. If the arterial pump is stopped for various reasons and the vacuum source is left on the venous reservoir, microbubble transgression can occur from the gas compartment to the liquid compartment of the oxygenator, creating another source of gaseous microemboli as soon as the arterial pump is turned on again [9, 12].

Arterial cannulation is usually via the ascending aorta. Exceptions, however, are frequent in the newborn with malformation of the ascending aorta (e.g. interrupted aortic arch and hypoplastic left heart syndrome [HLHS]). In that scenario, the ductus arteriosus is primarily cannulated to maintain body perfusion on bypass and the pulmonary arteries are snared to prevent runoff until an anatomic correction takes place.

The clinician must also be aware that femoral cannulation is not feasible in small children <15 kg because of the small vessel size. Thus, on repeat sternotomy, this method of establishing CPB is usually not an option and careful retrosternal dissection must take place.

Table 11.2 Cardiopulmonary bypass tubing volumes

Tubing diameter (in.)	Volume per meter length (mL/m)
1/2	126
3/8	71
1/4	33
3/16	18

Table 11.3 Cardiopulmonary bypass tubing sizes

Arterial and venous tubing sizes	Patient weight
3/16 in. arterial line, 1/4 in. venous line	<10 kg
1/4 in. arterial line, 3/8 in. venous line	<20 kg
3/8 in. arterial line, 3/8 in. venous line	<50 kg

The aortic cannula represents the smallest diameter in the pediatric CPB circuit. The bypass tubing is responsible for the large foreign surface area and priming volume. The strategic selection of tubing dimensions can reduce the volume effectively (Tables 11.2 and 11.3). For example, in a 3.5 kg newborn with an approximate blood volume of 300 mL, the addition of a cardiotomy suction line of 6.3 mm (1/4 in.) diameter and with a total length of 250 cm would require approximately one third of the patient's blood volume (82.5 mL) before reaching the reservoir.

Malposition of cannulas is particularly problematic in pediatric perfusion. Systemic perfusion may be adversely impacted when placement of either venous or arterial cannulas is not ideal. If a venous obstruction occurs, the consequences are magnified because of low perfusion pressures. If the IVC cannula causes venous obstruction in the splanchnic bed, increased hydrostatic pressure causes ascites, and reduced perfusion pressure results in significant renal, hepatic, and gastrointestinal dysfunction. Obstruction of the superior vena cava (SVC) may produce an increase in intracranial pressure and result in decreased cerebral perfusion pressure and cerebral edema. It is possible to observe preferential flow to one side of the cerebral circulation or down the distal aorta (Figure 11.3). Transcranial Doppler monitoring of cerebral flow velocity or cerebral oximetry can provide an early warning of altered flow patterns caused by cannula misplacement [11]. Cooling patterns demonstrating rectal cooling preceding nasopharyngeal cooling may suggest a disproportionate amount of pump flow being directed away from the cerebral circulation [13].

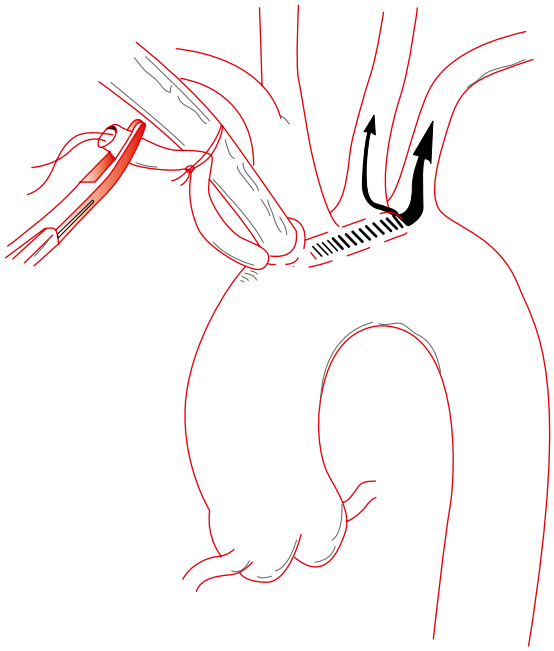


Figure 11.3 Malposition of the aortic cannula high in the ascending aorta. This cannulation technique is helpful for any surgery on the ascending aorta. Particular attention is needed to avoid preferential perfusion of the left cerebral hemisphere. Note the obstruction of flow to the innominate artery in this case. (Source: Gottlieb et al. [11]. Reproduced with permission of John Wiley & Sons.)

Pumps

The two pumps most commonly used for CPB are roller pumps and centrifugal pumps. Roller pumps have the advantages of simplicity, low cost, ease and reliability of flow calculation, and the ability to pump against high resistance without reducing flow. Disadvantages include the need to assess occlusiveness, spallation of the inner tubing surface, which potentially produces particulate arterial emboli, the capability of pumping large volumes of air, and the ability to create large positive and negative pressures. Centrifugal pumps offer the advantage of lesser air pumping capabilities, less ability to create large positive and negative pressures, less blood trauma, and virtually no spallation. Disadvantages include higher cost, the lack of occlusiveness (creating the possibility of accidental patient exsanguination), and afterload-dependent flow requiring constant flow measurement. In the setting of short-term CPB for cardiac surgery, it remains uncertain whether the selection of one pump over another is of clinical significance; most institutions employ roller pumps for congenital heart surgery.

Oxygenator

The efficiency of gas exchange in the natural lung is mainly attributable to the large surface area generated by the airway and circulatory networks and the low resistance to diffusion. These same features are essential to the design of an efficient artificial lung. Other necessary features of an ideal oxygenator include minimal trauma to blood, thromboresistance, minimal reaction with blood components, minimal generation of gaseous microemboli, the ability to maintain performance over long periods, low prime volume, consistent physical properties, reliability, ease of use, and low cost. The efficiency of a membrane oxygenator is two to three times less than that of the natural lung at rest, and about eight times less than the natural lung under conditions of maximal exercise. The primary limiting factor to efficient gas exchange in membrane oxygenators appears to be blood phase resistance to both O_2 and CO_2 diffusion. A second factor that has limited the use of microporous membranes in situations of long-term extracorporeal support is the progressive decrease in gas exchange function. The most common microporous

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membrane oxygenator design in clinical use is the hollow-fiber type in which the polypropylene membrane is formed into fibers that are bundled or woven together. The fibers are 200–250 µm in diameter and 10–15 cm long, and the membrane thickness is 25–50 µm. Although the existence of micropores in the membrane significantly increases the gas exchange of membrane oxygenators, long-term use results in the progressive wetting of the surface, plasma leakage through the pores, and subsequent deterioration of membrane performance, thus limiting its use to acute CPB procedures. The newest oxygenators incorporate an arterial line filter to reduce priming volumes.

Priming

Bypass prime composition and volume are adapted to the particular requirements of the patient. The composition, however, is often a matter of opinion and differences are as great as the number of pediatric heart centers. If there is a consensus, it is probably only with regard to reducing volumes to a minimum to reduce transfusion requirements and dilutional effects of the patient [8, 14].

Despite recent advances made in technology, the majority of neonates and infants still require perioperative transfusion of homologous blood components. The lower the body weight of the patient, the more banked blood products need to be added to the prime. To maintain colloid osmotic pressure and a minimal amount of coagulation factors, albumin and fresh frozen plasma (FFP) are added. The most suitable priming in neonates seems to be the combination of albumin or FFP and red blood cells in such proportions so as to maintain the hematocrit (Hct) at about 28–30% during normothermia. A few centers are still able to obtain fresh whole blood (<48 hours after donation) for neonates, but outcomes of studies using this technique vs. "reconstituted" whole blood (FFP plus packed red blood cells [PRBCs] from the same or different donors) are conflicting [10, 15, 16]. Albumin is reported to maintain colloid osmotic pressure (COP; normally around 20–25 mmHg) and to reduce fluid accumulation [8, 10, 17, 18] while adding FFP to the prime maintains COP increases the level of coagulation factors and reduces intraoperative transfusion requirements in complex neonatal and cyanotic cases [12, 19]. However, postoperative transfusion requirements are not affected despite higher fibrinogen concentrations and better thrombelastographic values at the end of CPB [9, 20]. The level of ionized calcium is adjusted, as all blood products contain significant amounts of citrate. This can lead to acute hypocalcemia and cardiac arrest with the initiation of bypass. In addition, added erythrocyte concentrates should be as fresh as possible (<3–5 days old) to avoid hyperkalemia and hyperlactatemia as side effects. The reasons for this suggestion are that the level of 2,3-diphosphoglycerate in stored red blood cells decreases, metabolic load increases (potassium and lactate levels by the end of the second day are up to 7–25 mmol/L [11, 21]), and the risk of complications with bypass is higher. The risk is particularly high in infants <5 kg if the prime contains irradiated blood [13, 22]. If the red blood cells (RBCs) in the prime are older than 5 days, a prime blood gas should be checked and corrected. Circulating and filtrating the prime for 20 minutes alleviates most of these problems. Alternatively, processing PRBCs via a cell saver is reasonable and may add additional benefits such as the avoidance of hyperglycemia, high citrate levels, and hyperkalemia [14–16, 23, 24]. In addition, lactate levels are reduced and microaggregates >20 µm are eliminated. Care must be taken to avoid using normal saline as a washing solution, as a hyperchloremic metabolic acidosis can be induced in newborns and infants. In addition, the use of cell-saving devices during pediatric cardiac surgery provides another means of reducing banked blood exposure [25]. A desirable practice is to adjust the prime composition in neonates and small infants to the patient's blood, with pH, Na^+, K^+, Ca^{2+} and temperature within narrow ranges.

PRBC requirements can be calculated on the basis of weight and starting Hct. The change in Hct, ΔHct, is calculated as follows:

$$\Delta\text{Hct} = \frac{(\text{Hct}_{\text{PAT}} \times \text{BV}_{\text{PAT}})}{\text{BV}_{\text{PAT}} + \text{PV}}$$

where HctPAT is patient hematocrit, BVPAT is the patient blood volume (see Table 11.4) and PV is the priming volume. The transfusion requirement is calculated as:

$$\text{PRBC (mL)} = \text{Hct}_{\text{DESIRED}} \times (\text{BV}_{\text{PAT}} + \text{PV}) - \frac{(\text{BV}_{\text{PAT}} \times \text{Hct}_{\text{PATIENT}})}{60\%}$$

where 60% is the average Hct of stored PRBCs. After initial prime composition, an Hct on the prime can be measured, and a further adjustment before CPB is made to achieve Hct in the goal range. In newborns, a goal Hct on the pump of 30–35% is maintained. Older patients or special circumstances (e.g., severe hypoxia) may require adjustments to a lower limit of around 25% or higher than 30% (severe hypoxia), even though both limits are controversial. Historically, many centers permitted marked hemodilution on CPB to avoid transfusion. Recent studies question this approach and provide evidence of improved neurological function when higher Hcts are maintained during CPB. A randomized controlled clinical study in infants undergoing CPB demonstrated adverse perioperative and developmental outcomes with extreme hemodilution [26]. This issue remains controversial, although the clinical data in support of higher Hcts of at least 25% are compelling [27, 28]. Also, hemostasis may be improved by higher Hct levels.

An interesting strategy described in recent years is utilizing a neonate's own umbilical cord blood (UCB) for prenatally diagnosed patients undergoing cardiac surgery with bypass [29]. UCB is collected in a sterile fashion in the delivery room, and with milking of the umbilical cord, 50–140 mL of UCB can be obtained. After sterile processing, the UCB can be utilized as whole blood, or separated into packed RBC and fresh frozen plasma components. UCB contains stem cells and other progenitor cells, growth factors, and cytokines, in addition to RBC. Theoretical advantages of UCB are lack of immunogenicity, high concentration of fetal hemoglobin to facilitate unloading of oxygen into the tissues, and potential benefits of the progenitor cells. Half of the collected blood can be used to prime the bypass machine, and half can be

Table 11.4 Estimated patient blood volumes by weight

Weight (kg)	Estimated blood volume (mL/kg)
<3 (neonate)	90
3–10	85
10–20	80
20–30	75
30–50	70
>50	65

used for post-bypass transfusion. Drawbacks to UCB include complexity of collection, bacterial contamination, and limited storage time. Small single-center studies from a few institutions are the only data available, but UCB appears to be safe. Larger studies with a more careful assessment of the fate of all of the cell types are needed before wider use of UCB for neonatal surgery.

KEY POINTS: BASIC BYPASS CIRCUIT SETUP

- The basic bypass circuit consists of the venous reservoir, the oxygenator/heat exchanger unit, roller pumps for perfusion, suction, and cardioplegia and the connecting tubing, cannulae, as well as monitoring and alarm devices.
- The oxygenator contains an integrated arterial filter.
- Priming for children <10 kg includes either fresh whole blood or reconstituted blood prime with PRBCs and/or FFP.
- Target hematocrits on bypass are >25% with a goal of >35% for neonates and complex cyanotic lesions or >28% for acyanotic lesions.

Differences between pediatric and adult CPB

Major differences need to be considered when dealing with the pediatric patient on CPB (Table 11.1). These include the degree of hemodilution, flow rates and perfusion pressure, temperature, cannulation, prime and blood gas management, ultrafiltration, hemodynamic management, and, in certain cases, the presence of aortopulmonary collaterals.

Hemodilution

Recent efforts to minimize circuit volumes have led to the development of smaller circuit elements. However, there continues to be a gross degree of hemodilution realized in the neonatal patient. This can be as much as three to 15 times the amount of hemodilution seen in an adult. For example, in a 3 kg child given 85 mL/kg, an estimated blood volume (EBV) of 255 mL contrasts with an average circuit prime volume of 300–400 mL. Thus, a prime : EBV ratio can exceed >2–3 : 1, or >100–150% of a neonate's blood volume.

In the average adult circuit, only a 25–33% dilution rate is realized. This degree of dilution necessitates the addition of donor blood up to a body weight of approximately 10 kg to maintain an adequate Hct for optimal oxygen delivery on bypass.

Perfusion pressures

Management of the pediatric patient undergoing CPB is made difficult by competing hemodynamic goals for the brain, heart, and viscera. The brain is protected from hypoperfusion by systemic vasoconstriction and pressure autoregulation. Optimal mean arterial pressure targets are not uniform. They depend on cerebral autoregulation and vasoreactivity. This varies by age and underlying conditions. Patients with prematurity, previous brain injury, underlying congenital heart disease, hypothermia, or patients on ECMO can have abnormal cerebral autoregulation which makes it difficult to optimize the brain perfusion pressures. Invasive measurements of cerebral blood flows are not feasible, but non-invasive continuous monitoring of pressure autoregulation may be performed using near-infrared spectroscopy (NIRS) as a surrogate of CBF by using the hemoglobin volume index (HVx). The HVx is a moving correlation between arterial blood pressure and blood volume measured by cerebral oximetry and is able to evaluate individual autoregulatory thresholds [30]. See Chapter 14 for additional detail.

Perfusion pressures in the neonate can be quite low, less than 30 mmHg. This is often due to the lack of reactivity of the neonatal vasculature or the presence of a shunt like a patent ductus arteriosus (PDA). With meticulous management of blood gases, Hct, temperature, and flow rates, the goal should be the minimal use of vasoconstricting agents (i.e. phenylephrine) to maintain ideal blood pressure. As a rule of thumb, perfusion pressure (MAP [mean arterial pressure] – CVP [central venous pressure]) goals in the neonate are 35–45 mmHg, and over the first 2 years of life, the target perfusion pressure increases to 45–50 mmHg. Although not yet validated by neurologic outcome studies, the lower limit of autoregulation as measured by the HVx in neonates averages about 30 mmHg in the first week of life and increases to about 40 mmHg by 30 days, with considerable variation [31]. At best, normal flow rates are combined with reasonable perfusion pressures to reach all tissue beds, including those that require a certain opening pressure for function (kidney, brain, splanchnic bed). One should also keep in mind that the lower limit of myocardial perfusion pressure is around 15 mmHg, calculated as MAP – CVP. This is relevant for diastolic pressures below 30 mmHg.

Flow rates

The flow rates for neonates are quite variable, ranging from 0 to 200 mL/kg/min. Deep hypothermic circulatory arrest (DHCA) is at one end of the spectrum, contrasted with high metabolic demands, vent return, circuit shunts, or patient collaterals, all of which contribute to the necessity of high flow rates at the other end. This can often exceed a cardiac index of 3 L/min/m^2. The flow rates are calculated on the basis of weight, but the perfusionist must adapt flows according to the individual case and to meet the demands. One strategy is to employ standard full flow rates in neonates and infants up to 10 kg of 150 mL/kg/min. With hypothermia and decreased metabolic demands, many centers will reduce flows to 80–100 mL/kg/min to reduce venous return to the field, lowering flows further to 25–50 mL/kg/min during deep hypothermia for intracardiac complex repairs.

AL Grawany

Recent data has demonstrated the feasibility of goal-directed, personalized CPB flow rates utilizing parameters such as mixed venous oxygen saturation (MVO_2) measured continuously in line from the CPB circuit, cerebral and somatic oxygen saturation measured by near-infrared spectroscopy, arterial blood gases, hemoglobin, and lactate concentration. Goals such as cerebral oxygen saturation (rSO_2) above 50%, maintaining somatic rSO_2 values higher than cerebral rSO_2, MVO_2 >70%, and lactate less than 2.5 mmol/L have been reported [32]. Bojan and colleagues retrospectively reviewed 180 neonatal surgeries and serum lactate values, and calculated oxygen delivery (DO_2, mL/min/m^2) utilizing CPB flow rates, hemoglobin concentrations, and PaO_2. [33] They determined a minimum DO_2 to maintain aerobic metabolism, indicated by a peak lactate concentration after aortic cross clamp removal <2.5 mmol/L, at normothermia and different levels of hypothermia. The average minimum DO_2 at 37 °C was 340 mL/min/m^2, a value significantly higher than older children and adults. Minimum DO_2 decreased linearly with temperature (Figure 11.4). The same group published a retrospective study of somatic to cerebral

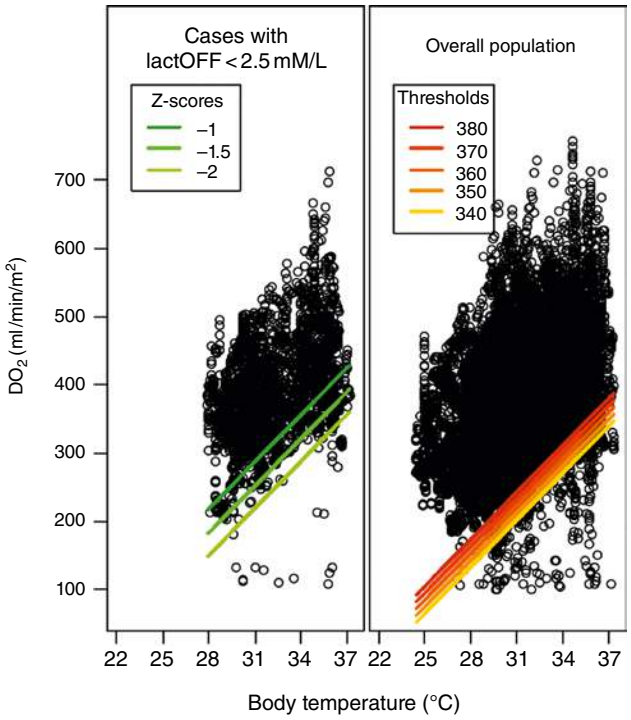


Figure 11.4 Oxygen delivery as a function of body temperature during aortic crossclamping. In the left panel are shown the observed oxygen deliveries (DO_2) in patients with first lactate after aortic crossclamp was removed (lactOFF) <2.5 mM, and the estimated −1, −1.5, and −2 DO2 Z scores, as a function of body temperature. In the right panel are the observed DO_2 values in the overall population, as a function of temperature, and several DO_2 thresholds tested for associations with lactate production. These were empirical thresholds chosen in an attempt to refine the −2 Z score. DO_2 threshold of 357 mL/min/m^2 was identified in the lactOFF <2.5 subgroup and found to be linked with lactate production. The final analysis revealed that the lowest threshold linked with lactate production and thought to represent the lowest suitable DO_2 during normothermic neonatal bypass was 340 mL/min/m^2. (Source: Bojan et al. [33]. Reproduced with permission of Elsevier.)

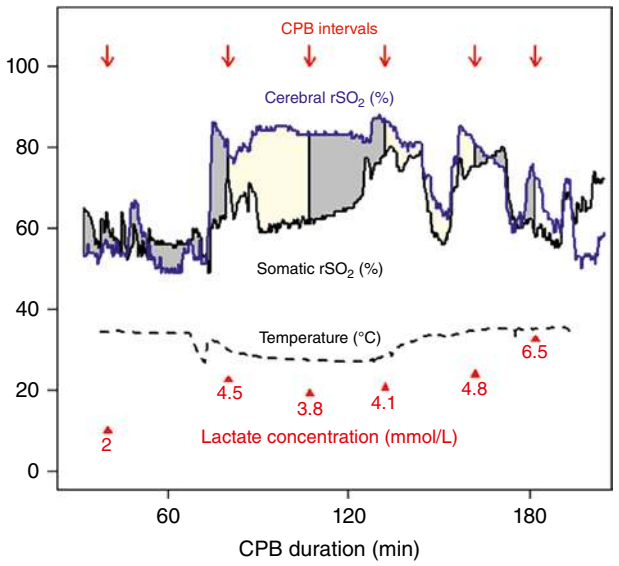


Figure 11.5 The somatic-cerebral NIRS gradient, lactate concentrations, and temperature during cardiopulmonary bypass in a neonate. For each time interval between two lactate measurements, the lactate concentration variation and the somatic-cerebral rSO_2 gradient were calculated. The somatic-cerebral rSO_2 gradient was the sum of all positive and negative areas resulting from excursions of the somatic rSO_2 above and below the cerebral rSO_2 and was calculated aby the trapezoidal method. rSO_2, regional oxygen saturation. (Source: Bojan et al. [34]. Reproduced with permission of Oxford University Press.)

rSO_2 difference during CPB in 24 neonates, and reported that there was a predictable increase in lactate concentration when the somatic to cerebral rSO_2 difference decreased or became negative [34] (Figure 11.5). Although potentially more complex than a standard flow rate specified according to weight or body surface area, combined with temperature, this approach of varying CPB flow according to oxygen demand may balance minimum oxygen delivery needs with the need to reduce flows to decrease blood return to the surgical field. More data, along with outcome studies, are needed to determine whether the goal-directed approach has any advantage over current methods.

Blood gas management

It is the current practice in some institutions to employ pH-stat management in all cases in which temperatures are taken to hypothermic levels. In this temperature-corrected strategy, the PCO_2 remains unchanged from 37 °C (40 mmHg). This strategy allows for cerebral vasodilation and more even cooling. The corrected PCO_2 ranges at 37 °C can be >80–100 mmHg.

Aortopulmonary collaterals

Uncommon in adults, but fairly common in patients with chronic cyanosis with decreased pulmonary blood flow, aortopulmonary collaterals can be a challenge. It can be difficult to empty the heart. Flow rates are frequently affected, and temperatures may need to be lowered substantially to

accommodate lower bypass flows to reduce blood return to the operative field. Flows may need to be decreased in conjunction with the use of vasodilating agents. Phentolamine 0.1 mg/kg and nitroglycerine are the drugs of choice during cooling and rewarming, titrated to effect. Phenylephrine is contraindicated and would only enhance collateral flow.

Temperature ranges

As a very basic comparison, there is a trend toward conducting adult cases at tepid or normothermic temperatures while many neonatal cases are still utilizing cold temperatures with or without DHCA. However, more and more neonatal cases are performed at mild hypothermia. The perfusion considerations are multiple, and this topic is discussed in a separate section on hypothermia and DHCA.

Glucose management

It is of utmost importance to maintain euglycemia in the neonate. Although there are increased glycogen stores in the neonatal myocardium, there are low hepatic glycogen stores. Exogenous glucose may be necessary in the early neonatal period to maintain normal glucose levels and should be continued into the pre-bypass period.

Perfusion considerations on CPB are directed at efforts to maintain normal glucose levels such as washing packed cells or minimizing glucose content in cardioplegia or intravenous (IV) fluids. When glucose levels are greater than 300 mg/dL, a saline hemodilutional washout with the hemoconcentrator is utilized. Frequent monitoring is recommended. Levels should be maintained at approximately 150 mg/dL just prior to DHCA.

Hyperglycemia worsens neurological injury, as elevated glucose levels result in the increased anaerobic metabolism of glucose and increased lactic acidosis. This leads to further depletion of ATP. Hypoglycemia alone can be treated but coupled with hypothermia, cerebral blood flow may be compromised by altering autoregulation. This can be further exacerbated with hyperventilation, as this may occur in weaning a patient with pulmonary hypertension from CPB. Overall, tight glycemic control (blood glucose level in the range of 80–110 mg/dL) is not indicated in children as the outcome was not any different from standard care in the intensive care unit (ICU) [35]. Hyperglycemia was not associated with lower neurodevelopmental outcomes at 8 years of age in the Boston Circulatory Arrest Study. However, lower glucose measurements below 90–100 mg/dL after CPB were associated with a higher risk of electroencephalogram (EEG) seizures. The authors speculate that limiting glucose as an important energy substrate for the neonatal brain, which may have increased requirements under conditions of low CPB flows or DHCA, may be a reason for this association [36]. In a more contemporary study of 93 neonates undergoing the arterial switch operation, patients with more than 50% of the intraoperative and early postoperative periods spent at glucose values between 80 and 110 mg/dL had more perioperative complications than those with >200 mg/dL more than 50% of the time [37]. The practice of many pediatric cardiac anesthesiologists is to maintain plasma glucose levels in the 100–200 mg/dL range for neonates and small infants.

Equipment

One circuit size for the adult patients at a given institution can adequately provide flows for patients from 50 kg and more. Most pediatric centers employ two or three circuits on the basis of the patient's weight, procedure, and flow requirements.

Ultrafiltration

Utilization of ultrafiltration in some form, whether it be conventional or modified, is seen in >90% of our neonatal and pediatric cases. Several system modifications may be necessary to allow for these options.

KEY POINTS: DIFFERENCES BETWEEN PEDIATRIC AND ADULT CPB

- The major differences between pediatric and adult CPB are the degree of hemodilution, flow rates, and perfusion pressures.
- Hemodilution is exaggerated and can reach more than 150% of the patient's blood volume.
- Flow rates are in the range of up to 200 mL/kg/min or an equivalent cardiac index of 3.0 L/min/m^2 and higher can be found in the neonate.
- Aortopulmonary collaterals can be a challenge during bypass and should be managed with vasodilators and increased flow rates.
- pH-stat is the preferred method of blood gas management during cooling in pediatric cases using deep hypothermic circulatory arrest.
- Glucose management with targets of 100–200 mg/dL is desirable.

Management of pediatric CPB

Stages of CPB

Cardiac cases using CPB can be divided into several basic phases: pre-bypass period and anticoagulation, bypass period with initial cooling, cross-clamping and myocardial protection, reperfusion of the heart, separation from CPB, modified ultrafiltration and hemostasis, and, lastly, sternal closure and transfer to the ICU.

Pre-bypass period

The pre-bypass period begins with surgical incision and lasts through to initial dissection and preparation for cannulation. During this period, transesophageal echocardiography (TEE) is performed to confirm the diagnosis and establish a basis for post-bypass comparison. Baseline activated clotting time values are obtained and metabolic abnormalities are corrected. Cannulation of the great vessels just prior to CPB can often precipitate arrhythmias, hypotension, and arterial desaturation, especially in small infants and children. Ventilation may need to be limited to minimize lung excursion to allow precise

cannulation in small infants. Coordination with the surgeon is particularly important. Hemodynamic stability is maintained by cautious fluid administration and small boluses of vasopressors, as deemed necessary. After placement of the aortic cannula, pressure in the aortic root is measured by the perfusionist through the cannula *in situ* and should be close to the MAP of the patient. A small volume infusion of 2–5 mL/kg is often used at that point to ensure unobstructed aortic cannula flow before bypass. If the aortic cannula is already in place, it is common practice to coordinate the administration of volume between the anesthesiologist and perfusionist while the surgeon completes cannulation.

Anticoagulation and hemostatic management

Development of the coagulation system is incomplete at birth and continues in the postnatal period until the age of about 6 months. This increases the risk of bleeding disproportionately in the neonatal and infant group up to 1 year or approximately 8 kg of weight [38–40]. Coagulation in cyanotic infants may be particularly impaired secondary to polycythemia, lower fibrinogen levels, low platelet count and abnormal platelet function [41], decreased concentrations of factors V, VII, and VIII, and increased fibrinolysis [42, 43].

Of particular importance is the role of antithrombin (AT) levels that do not reach adult values until 3–6 months. This low level of AT may reduce the ability of heparin to provide anticoagulation adequate to prevent thrombin generation during CPB in infants [38, 42, 44–46] and an exaggerated inflammatory response may occur [38, 42, 43, 47, 48]. Infants may require an initial heparin dose of 400 units/kg or higher. Manlhiot and colleagues reported AT levels and heparin consumption in 90 infants <1 year undergoing CPB surgery.[49] Baseline AT levels were strongly dependent on age, with lower levels in neonates (Figure 11.6). Lower AT levels were also associated with lower heparin response as measured by anti-factor Xa levels and higher heparin consumption (Figure 11.7A and B). It has also recently been shown that in infants with CHD, levels of other thrombin inhibitors are depressed compared with healthy infants. This may partially explain the high levels of thrombin generation during infant CPB. The coagulopathy induced by CPB affects children more profoundly than adults. There are many factors implicated, including hemodilution, contact activation, and initiation of a systemic inflammatory response. Despite large doses of heparin during CPB, heparin does not block thrombin generation completely but partially inhibits thrombin after it is produced. Thrombin is continuously generated, and a consumptive coagulopathy is initiated [44, 46]. The lower potential of newborn plasma to generate thrombin might, in part, downregulate thrombin markers during CPB. This, however, does not seem significant enough to completely prevent the subsequent reperfusion-induced thrombin peak [42, 43, 47–48, 50]. Thromboelastography (TEG) has actually shown that neonates and infants develop faster and stronger clots than adults [38–40, 51]. In addition, acquired coagulation defects in 58% of non-cyanotic and 71% of cyanotic infants have been reported [41, 52–54]. If thrombin formation could be completely inhibited during CPB, the consumption of coagulation proteins and platelets could largely be prevented. Initial heparin doses range from

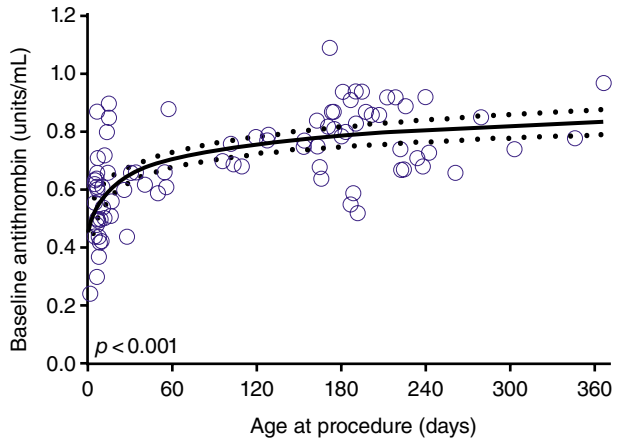


Figure 11.6 Antithrombin levels by age at surgery. Blue circles represent individual patient values; solid lines show the estimates from regression models, and dotted lines are the 95% confidence interval. Manlhiot et al. [49] / Reproduced with permission of Elsevier.

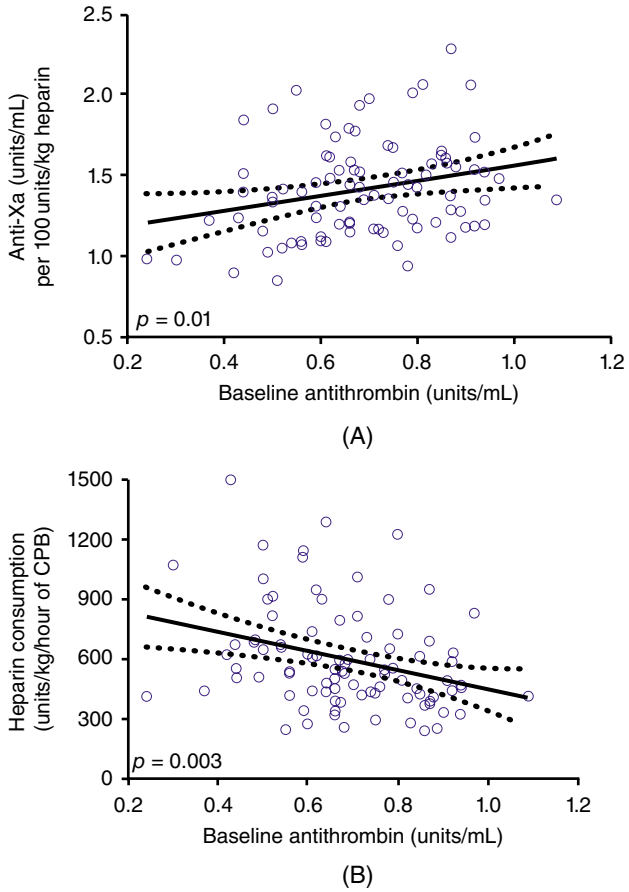


Figure 11.7 (A) Association between preoperative AT level, and heparin response as measured by anti-factor Xa level per 100 units/kg heparin. (B) CNEW. Association between preoperative AT level, and heparin dose throughout CPB, indexed for weight and duration of CPB. Blue circles represent individual patient values; solid lines show the estimates from regression models, and dotted lines are the 95% confidence interval. (Source: Manlhiot et al. [49] / Reproduced with permission of Elsevier.)

300–400 units/kg bolus before cannulation to 200–400 units/kg in the circuit, and to 50–100 units/kg ongoing administration every 30–120 minutes. Heparin's peak therapeutic effect occurs within 2 minutes. CPB may delay the peak effect by 10–20 minutes from hypothermia or hemodilution. Plasma binds 95% of heparin with some uptake by the extracellular fluid, alveolar macrophages, splenic/hepatic endothelial cells, and vascular smooth muscle. The plasma half-life is dose-dependent (i.e. 126 ± 24 minutes at a dose of 400 units/kg vs. 93 ± 6 minutes at a dose of 200 units/kg) [38–40, 55]. Heparin is metabolized by the reticuloendothelial system and is eliminated by the kidneys. Hypothermia and renal impairment, but not hepatic impairment, delay elimination. A roughly linear relationship exists between heparin dose and the activated clotting time (ACT) if certain criteria are maintained [41, 56], namely normal ATIII and factor XII activities, normothermia, near-normal platelet function, a platelet count >50,000/dL, and fibrinogen concentration >100 mg/dL. However, in children, the correlation is rather poor [42, 43, 57]. An ACT is measured before heparinization and repeated a minimum of 3 minutes after giving heparin. CPB is not initiated until an adequate ACT or heparin level is confirmed.

Given the variability in the ACT, heparin concentration can also be measured directly. A two-point (straight line) dose-response curve assists in judging how much additional heparin to administer. Acceptable levels during CPB are 2–4 units/mL, and in the newborn population up to 6 units/mL. This regimen increases required heparin doses on CPB but results in lower protamine doses and less blood loss [45, 58]. The optimum method of assessing adequate anticoagulation during CPB in children has thus not yet been defined and much work is required in this area. The use of heparin-coated biocompatible perfusion circuits is probably helpful in reducing the degree of activation of the coagulation system in children [47, 48, 59, 60], but it is rather expensive and has not gained wide acceptance.

The optimal ACT for CPB is controversial. Although the minimum recommended ACT is 400 seconds, other authors recommend 480 seconds [44, 46, 61], as heparin only partially inhibits thrombin formation. This is done to minimize the consumptive coagulopathy that may result from barely adequate anticoagulation. Failure to achieve a satisfactory ACT may be due to inadequate heparin or low concentrations of ATIII, or "heparin resistance." [49, 62]. Increases in acute-phase reactant proteins such as factor VIII and fibrinogen commonly shorten the APTT and may appear as heparin resistance. If 500 units/kg of heparin fail to achieve an adequate ACT, ATIII deficiency becomes more likely and FFP or recombinant ATIII (30 IU/kg) [50, 55] is necessary to increase antithrombin concentration.

Heparin dosing, ACT targets, and protamine reversal dosing were first established in the 1950s and published in a landmark paper by Keats, Cooley, and Telford from Texas Children's Hospital [63]. Today more than 60 years later, this approach is still used in most congenital heart surgery centers. The need for alternatives to heparin for bypass anticoagulation has been discussed for years, in part because of not only the problem of heparin-induced thrombocytopenia predominantly seen in the adult population but also the ongoing issue of bleeding and thrombosis with heparin in pediatric cardiac surgery despite many advances in monitoring and treatment of coagulopathy. Direct thrombin inhibitors such as bivalirudin can be utilized for pediatric cardiopulmonary bypass; the drawbacks with this drug are several and include that there is no reversal agent and it has a half-life of approximately 25 minutes, so a loading dose and infusion are necessary. In addition, bivalirudin lacks a widely available point-of-care test. The ecarin clotting time for bivalirudin is primarily a research tool. The ACT is used as a rough guide to anticoagulation, along with a viscoelastic method of coagulation assessment. Hasija and colleagues published a randomized, controlled safety and efficacy study of bivalirudin vs. heparin in 50 acyanotic patients aged 1–12 years who were undergoing corrective cardiac surgery with bypass[64]. Furthermore, 400 units/kg of heparin plus pump prime, vs. 1 mg/kg bilvalirudin bolus followed by 2.5 mg/kg/hour, and a pump prime dose, was studied. Using a 480 second ACT goal, 1 of 25 heparin patients required extra dosing as compared to 13 of 25 bivalirudin patients. ACT returned to baseline after protamine in the heparin group but remained elevated for an average of 2 hours in the bivalirudin group. With viscoelastic testing, heparin prolonged the onset of clotting, decreased the rate and strength of clot formation, and inhibited platelet function to a greater degree than bivalirudin. Duration of surgery was longer in the bivalirudin group, but chest tube drainage and transfusion were similar. No adverse events occurred.

More pediatric cardiac patients are arriving in the operating room (OR) because cardiac surgery is being anticoagulated with direct thrombin inhibitors. Patients on ventricular assist support achieve better and more accurate anticoagulation with these agents, namely bivalirudin, and this agent is now standard of care in many programs for a ventricular assist device (VAD), and even some ECMO patients [65, 66]. Bivalirudin infusion is usually discontinued prior to or on arrival to the OR. It is not thought to affect anticoagulation or hemostasis with heparin on bypass because of its relatively short half-life, but increased bleeding may occur with surgical dissection prior to bypass.

Initiation of CPB and flow requirements

After heparinization and cannulation, CPB is initiated by opening the venous outflow cannula to the reservoir. Slow decompression of the heart and maintaining a minimal output of the beating heart reduce the drop in blood pressure due to the hemodilution. Based on weight or body surface area, a flow requirement is calculated. The cardiac index is approximately 25–50% greater than that of an adult. For newborns, a flow of 2.6–3.2 L/min/m^2 is recommended, and for infants, a flow of 2.4–2.6 L/min/m^2 is sufficient. If normothermic CPB is chosen, flow rates in the range of 3.0–3.5 L/min/m^2 are required [51–53, 67]. This can be reduced during hypothermia (Figure 11.8) [68]. Infants have a much more compliant vasculature, which results in lower perfusion pressures on CPB. Causes of severe hypotension after initiation of bypass can be the presence of hemodynamically relevant shunts (e.g. major aortopulmonary collateral arteries) previously placed systemic to pulmonary artery (PA) shunt or a PDA, which both lead to a circulatory steal in the systemic circulation, requiring higher flows and possibly early

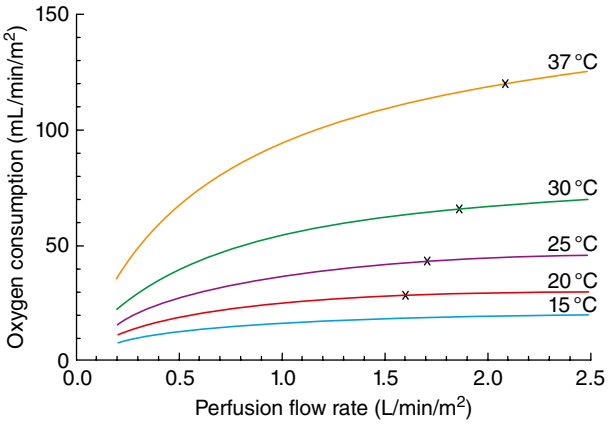


Figure 11.8 Nomogram relating oxygen consumption to perfusion flow rate and temperature. X indicates clinical flow rates used by Kirklin and Barrett-Boyes [68]. (Source: Kirklin and Barrett-Boyes [68]. Reproduced with permission of Elsevier.)

control by the surgeon. Increased bronchial and non-coronary collateral flow draining into the left atrium can be a particular problem, especially in cyanotic children, with a resultant significant negative impact on myocardial protection during periods of aortic cross-clamping. Because of the small and easily obstructed vena cavae in infants, careful assessment for venous obstruction is carried out immediately after initiation of bypass. The patient's head and face are assessed for signs of venous obstruction, including plethora and cyanosis of the scalp and face, distended fontanelle, and decrease in cerebral oxygen saturation to levels below the baseline. If a central venous catheter has been placed with its tip in the SVC, pressures should be low (i.e. <5 mmHg) and at times are negative if the placement is adjacent to the SVC cannula. Venous return judged by the volume in the venous reservoir is continually monitored by the perfusionist, with a sudden decrease prompting communication with the surgeon to investigate the cause.

The adequacy of perfusion is monitored by the usual parameters. These are MAP, the in-line measurement of mixed venous saturation, pH, base excess, and the regular testing of blood for heparin levels and lactate and other indices of end-organ perfusion (e.g., urine output, somatic and cerebral oxygenation values [NIRS for example]). (See above under flow)

Cooling and temperature management

Systemic cooling is often utilized for myocardial, cerebral, and other end-organ protection. Hypothermia is usually classified as mild (32–36 °C), moderate (24–32 °C), or deep (18–24 °C). In general, lower temperatures are used for more complex operations that carry a greater potential for requiring periods of low-flow bypass or circulatory arrest. Cooling is primarily achieved through the heat exchanger in the bypass circuit, although surface cooling with lower ambient air temperatures or forced-air warming systems set to lower temperatures is used in some institutions. Infants have a high ratio of surface area to body weight. Infants also have an immature thermal autoregulatory center. Because of these factors, wide fluctuations in body temperature occur easily. Warming and cooling on bypass occur much more readily. If the clinician is not careful, cooling can occur too rapidly, and deep brain structures may become dangerously cold. There is evidence to suggest that cooling too rapidly is deleterious to neurological function. Thus, it is important to cool slowly, evenly, and completely, and most investigators recommend at least 20 minutes of cooling if circulatory arrest is used (i.e., no faster than 1 °C/min) [69]. The opposite is also true. It is very easy to warm too rapidly and for hyperthermic overshoot to occur. Recent data suggest that hyperthermia can be very damaging, and temperature differences of even 1 or 2 °C are highly significant [70]. Monitoring should include nasopharyngeal, rectal, and arterial inflow temperatures. Rewarming the patient should occur at less than 8 °C temperature difference between the heat exchanger and patient blood temperature, with maximal inflow temperatures of 37.0 °C to avoid the formation of any micro air bubbles [71–73]. Special bypass techniques such as regional cerebral perfusion (see later) have been developed to avoid the necessity of using DHCA and may also be performed during this time.

In recent years, a number of centers have reported normothermic or mildly hypothermic bypass for a variety of congenital cardiac operations including some more complex neonatal surgeries such as the arterial switch operation [74]. Theoretical advantages include time saved by avoiding cooling and rewarming, improved coagulation and hemostasis, better oxygen and glucose transport in the neonatal brain, cellular membrane stability, better ATP production and utilization, and preservation of cerebral autoregulation. Despite the theoretical advantages, a meta-analysis of seven randomized controlled trials in pediatric patients revealed no differences in duration of CPB or aortic crossclamp, or in lactate or creatinine concentrations [75]. Corno and colleagues published a retrospective review of 99 patients <2 years of age undergoing normothermic (>35 °C) vs. hypothermic (28–34 °C) bypass, matched for cardiac lesion and surgical procedure [76]. They reported earlier extubation, shorter ICU stay, and lower transfusion requirement in the OR and ICU in the normothermic patients. Limitations of this study were its retrospective single-center nature, imperfect matching of patient groups, and small sample size. Neurodevelopmental follow-up of the cohort at 2–3 years after surgery revealed no differences between groups across multiple tested domains [77]. From the data reported so far about normothermic bypass for a variety of congenital operations, this approach would appear to be safe, but not to consistently lead to improved early clinical outcomes or shorter operating times.

Aortic cross-clamping, myocardial ischemia, and protection

Repair of most congenital heart lesions is becoming more feasible. Perioperative myocardial damage remains the most common cause of morbidity and mortality after successful surgical repair. Thus, effective myocardial protection assumes an even greater role than in the adult, as perioperative insults are less well tolerated and more difficult to treat. Neonatal hearts may be difficult to protect because of immaturity, cyanosis, hypertrophy of the right ventricle, complex coronary artery pattern, and duration of ischemia to achieve a good repair.

The neonatal heart is ultrastructurally immature. Myofibrils are arranged in a disorderly fashion and have a smaller percentage of contractile proteins than do those in adults (30 vs. 60%) [78]. The immature heart shows fewer mature mitochondria and a lower oxidative capacity [79]. Control of myocardial contractility in infants depends more on adrenal function and circulating catecholamines than on direct autonomic influences. There are also differences in myocardial calcium metabolism. In the mature myocardium, the sarcoplasmic reticulum is the predominant source of calcium ion for excitation-contraction coupling, but the sarcoplasmic reticulum is poorly developed in the immature heart (see Chapter 9). Because the neonatal myocardial cell is deficient in T-tubules, it is incapable of internal release and reuptake of calcium for contraction and instead depends heavily on transmembrane calcium transport for myocardial contraction. These differences in calcium handling by the cell provide some explanation for the clinical observation that newborns require greater serum ionized calcium levels for optimal myocardial contractility. Experimental evidence suggests that the newborn myocardium tolerates ischemia and reperfusion better than the adult heart. However, in practice, pediatric patients undergoing cardiac surgery have a greater incidence of low cardiac output postoperatively than adults. The discrepancy between the experimental evidence and the clinical experience may be related to the cardiac anomalies involved. Ventricular hypertrophy and cyanosis are common, and the hypertrophied heart has been found to have decreased subendocardial blood flow [80] and lower concentrations of high-energy phosphates before arrest. Chronic cyanosis has been associated with a decreased threshold for anaerobic metabolism during stress [81], diminished myocardial reserve [82], asynchronous left ventricular wall motion [83], and downregulation of β-adrenergic receptors [84]. Reoxygenation injury with the release of oxygen free radicals upon initiation of CPB can further exacerbate the pre-existing injury [85]. The abrupt increase in oxygen levels on bypass in chronically hypoxic infants leads to the loss of antioxidant reserve capacity and subsequent loss of myocardial function. Preventive measures include leukodepletion of blood prime, use of in-line arterial filters, and normoxic management (PaO_2 of 80–100 mmHg) initiating bypass. Over the course of 10–20 minutes, the fraction of inspired oxygen ratio (FiO_2) can be increased to obtain PaO_2 levels in the usual 100–150 mmHg range. As blood is fully oxygenated at such levels, further increases in oxygen levels only confer minimal increases in the oxygen content of the blood.

Finally, many congenital cardiac procedures require an incision of the ventricular muscle, which markedly changes the geometry of the chamber and induces focal edema.

The cornerstone of myocardial protection in pediatric cardiac surgery is hypothermia. Systemic hypothermia is, to some degree, used in nearly all congenital cardiac repairs. It is particularly important in cyanotic infants with increased non-coronary collateral flow to the heart.

Myocardial protection can be problematic in these cases because of cardioplegia washout and rewarming of the myocardium. Because systemic hypothermia allows reduced flow rates, it decreases myocardial collateral flow. Blood cardioplegia is often used in adults, but its advantages may be lost in infants undergoing deep hypothermia. However, if greater cardioplegic temperatures are used (warm cardioplegia), there is a clear advantage to the use of blood cardioplegia [86]. The optimal electrolyte composition of cardioplegia for pediatric patients is controversial. There is great institutional variation among solutions used. A certain amount of calcium is necessary in the solution to prevent the severe injury that may result from calcium paradox [87]. However, excessive amounts are deleterious. The addition of magnesium, a natural calcium antagonist, may solve this dilemma. Increasing the ionized magnesium level has been shown to improve postoperative rhythm stability and reduce calcium-induced mitochondrial dysfunction during reperfusion. Thus, in the absence of magnesium enrichment, hypocalcemic cardioplegia results in adequate myocardial protection in stressed hypoxic hearts. Magnesium was particularly beneficial during normocalcemic cardioplegia solution [88].

In addition to the specifics of cardioplegia administration reviewed in the following, a multifaceted approach to myocardial protection is taken by many institutions. For example, bypass prime composition is adjusted to closely match the patient's blood with regard to pH, serum Na^+, K^+, Ca^{2+}, and temperature. Initiation of bypass in a neonatal heart with cold, acidemic, hypocalcemic, hyperkalemic prime is a significant stress-increasing risk of inadequate myocardial protection. Gentle surgical handling of the heart by the primary surgeon and assistants is also felt to play a role, with excessive traction felt to disrupt the delicate fibrous skeleton of the heart, rendering less efficient the coupling of the myofibrils to mechanical force transduction of the heart. Gentle handling of the myocardium also lessens the risk of arrhythmia such as ventricular fibrillation, which on bypass represents an ischemic state of the heart. Monitoring carefully for the return of any cardiac electrical activity is important, giving consideration to more frequent cardioplegia dosing. Aggressively treating ventricular tachycardia, especially fibrillation, on bypass is very important. Meticulously maintaining venous drainage with proper cannula size selection and positioning, as well as venting of the left side of the heart prevents ventricular distension and subendocardial ischemia. Maintaining cold myocardial temperatures with ice slush application is also utilized to preserve a low-energy consumption state.

There is some evidence that volatile anesthetics can provide a degree of myocardial preconditioning when administered before CPB, in the setting of adults undergoing coronary bypass surgery. The cellular mechanisms are complex but are demonstrated to include mitochondrial and sarcolemmal potassium-ATP channel opening, transcription factors (NF-KB, HIF-1 alpha), new proteins (iNOS, COX-2), and mediators (NO, PGE, neutrophil inhibition). There is limited pediatric data, and no clinical studies have been published; hence, it is not clear whether this strategy is effective for neonatal and infant myocardial protection [89].

Induction and maintenance of cardioplegic cardiac arrest

Two basic methods of cardioplegic arrest are used: blood cardioplegia or crystalloid cardioplegia. The superiority of either method is still controversial [90].

Histidine-tryptophan-ketoglutarate (HTK), an intracellular crystalloid solution, has been widely used clinically for cardioplegic arrest during cardiac surgery. The HTK solution can offer sufficient cardiac protection to the neonatal heart for up to 2 hours of ischemia and provide equivalent myocardial protection to multidose cold blood cardioplegia with reduced transfusion requirements [91]. However, clinically significant hyponatremia can occur and severe fluctuations in sodium concentration should be corrected [92]. During induction, some institutions use warm blood cardioplegia with amino acid supplementation in stressed, hypoxic hearts to recover the intracellular energy stores before arrest [93]. This results in complete preservation of myocardial function, particularly in the chronic, hypoxic heart that might become ischemic under situations of stress.

Del Nido Cardioplegia solution has been increasingly used in congenital heart surgery in the past decade [94]. It is a 1 : 4 by volume blood: Crystalloid (Plasmalyte-A) solution containing potassium (~26 mEq/L), mannitol (~3.3 g/L), magnesium (~2 g/L), sodium bicarbonate (~13 mEq/L), and lidocaine (~130 mg/L). This solution is cooled and delivered at 8–12 °C, producing myocardial hypothermia to reduce oxygen consumption and promote myocardial preservation. The 20% by volume fully oxygenated patient blood supports aerobic metabolism for a finite period and also supports anaerobic glycolysis by providing buffering properties. Mannitol scavenges oxygen free radicals, reduces myocardial edema, and promotes osmotic diuresis. Magnesium acts as a calcium channel blocker, preventing the intracellular accumulation of calcium and diastolic dysfunction. Sodium bicarbonate and the Plasmalyte-A solution maintain neutral intracellular pH. The high potassium concentration produces a reliable depolarized diastolic arrest, and lidocaine acts as a sodium channel blocker and increases the refractory period of the cardiac myocyte.

Del Nido cardioplegia solution is administered antegrade as a single dose (20 mL/kg) during aortic clamping and has shown to provide safe myocardial protection with a longer period of arrest of up to 90 minutes. A dose of 10 mL/kg can be used for shorter crossclamp times of 30–45 minutes. Some centers re-dose at 60 minutes with a full or half dose, depending on the anticipated duration of crossclamping. This allows a bloodless operative field with less interruption compared to intermittent multidose cardioplegia. Single dose cardioplegia has been shown to have a higher rate of return to spontaneous rhythm, but no significant improvement in morbidity or lower requirement in inotropic support. Surgeon preference, anticipated aortic crossclamp duration, and case complexity should determine the selection of cardioplegia when planning procedures.

After aortic cross-clamping and sequestration of the coronary circulation, cardioplegia is generally administered in an antegrade fashion into the aortic root. As the neonatal heart lacks stenotic lesions, adequate distribution is not an issue. Perfusion pressures should be in the normal range of diastolic blood pressures and should not be higher than 30–50 mmHg. Higher pressures can lead to myocardial edema, particularly in the neonatal hypoxic heart [95]. The need for multidose cardioplegia in infants is controversial [96].

Myocardial collaterals are more important in neonatal hearts and can quickly lead to rewarming of the myocardium. Profound hypothermia or the reduction of flow can only provide limited additional protection, as other vital organs can be compromised (brain, kidney). Periodic reapplication of blood cardioplegia at intervals of 10–20 minutes counteracts non-coronary collateral washout.

Retrograde cardioplegia is utilized by some surgeons in selected situations, including cases that include an open aortic root and coronary artery translocations or transfers [97]. These include Ross procedures, arterial switch operations, and aortic root replacements. Retrograde cardioplegia is also used in some cases of severe aortic insufficiency where the ability to arrest the heart with standard aortic root cardioplegia is impaired. A small cannula, i.e. 6 Fr., is placed under direct vision into the coronary sinus, and cardioplegia is infused at pressures not exceeding about 50 mmHg. Because pediatric patients rarely have coronary stenosis, retrograde cardioplegia is used infrequently, and many surgeons prefer to avoid it altogether. Instead, the aortic root is opened immediately after cross-clamping, and cardioplegia solution is infused directly into each individual coronary artery ostia with special cannulae.

Reperfusion

Reperfusion is considered the phase when the coronaries are reperfused with regular systemic blood flow after cross-clamp removal and the patient is fully warmed. A few minutes before cross-clamp removal, lidocaine and magnesium sulfate may be administered to reduce the incidence of ventricular arrhythmias often seen after unclamping. Before aortic cross-clamp removal, TEE can be used to assist the surgeon in de-airing maneuvers, which may include manipulation of the heart and "milking" any intraventricular air through the aortic valve and out of the cardioplegia cannulation site. The patient may be positioned in Trendelenburg position before cross-clamp removal to avoid air bubbles being ejected into the cerebral circulation. This period is an important time in the course of cardioplegic arrest, as many mechanisms of cellular damage are completed during reperfusion. Optimally, normal sinus rhythm and myocardial contractility are restored during this time, while the patient is slowly rewarmed. In adults, reperfusion with warm blood before unclamping the aorta improved metabolic and functional recovery. Substrate-enriched reperfusion with the amino acids aspartate and glutamate, however, results in full recovery of function in infants [98]. Depending on the total ischemic time of the heart (aortic cross-clamp time), the heart requires time to restore the ATP stores in the myocardium. In general, 10–15 minutes are considered the minimum time requirement. For longer cross-clamp times, 25% of the time is considered appropriate as reperfusion time at our institution. Some centers administer calcium chloride 5–10 mg/kg into the CPB circuit 10–15 minutes after aortic unclamping to counteract the effect of higher magnesium concentrations from cardioplegia washout. The release of the cross-clamp often leads to a drop in blood pressure due to the higher release of anaerobic metabolites from the heart which causes vasodilation to a greater degree compared with the adult. This hypotension should not be treated by the administration of calcium at this point to reduce the risk of immediate reperfusion injury. In addition, at this time air can be ejected

into the right coronary artery, resulting in acute ischemia with ST-segment elevation and poor myocardial contractility; this is best treated with higher perfusion pressures and adequate time on CPB to allow passage of air through the coronary system and recovery of the myocardium. Calcium chloride 10–20 mg/kg can be administered to the CPB circuit or to the patient immediately before separating from bypass to correct the slight hypocalcemic state of CPB and improve myocardial contractility, but it should be avoided during the first 10–15 minutes of reperfusion of the heart. Additional doses of calcium are added to maintain normal levels of ionized calcium after bypass in neonates and infants, particularly as calcium and other electrolytes are lost quickly through the use of modified ultrafiltration and the infusion of citrate-rich blood products.

Separation from CPB and post-bypass phase

During rewarming, surgery is completed, and inotropic and vasoactive agents are started, but only after the ECG and myocardial contractility have improved to near normal. The rationale is that increasing myocardial oxygen demand too early in the post-ischemic heart may be detrimental. Ventilation commences after manual ventilation lung recruitment maneuvers, administration of nebulized β-agonist agents, if indicated, and thorough suctioning. The lungs are inspected visually if the pleura have been opened for complete inflation and deflation and any areas of atelectasis are addressed with inspiratory holding breaths near the patient's vital capacity. Severe ventilation problems may rarely need to be assessed with fiberoptic bronchoscopy for accurate assessment of endotracheal tube placement, and further suctioning of secretions. Hemofiltration and blood transfusion are used to achieve the desired Hct. Pressure transducers are re-zeroed and leveled. Left atrial and/or PA monitoring lines, if indicated, are placed at this time, as are temporary atrial and/or ventricular pacing wires. Forced air warming devices, circulating water mattresses, and ambient temperature are adjusted to desired levels. If the patient is incompletely rewarmed before separation from CPB, a significant temperature drop with the precipitous post-bypass reduction in core body temperature can occur ("afterdrop"). This may lead to vasoconstriction, shivering, increased oxygen consumption, and acidosis. However, post-ischemic hyperthermia can lead to delayed neuronal cell death and predispose to arrhythmias such as junctional ectopic tachycardia [99]. Mild degrees of hypothermia and certainly the avoidance of hyperthermia are essential in the perioperative period [100]. In the pediatric patient group, rectal temperature mostly reflects the peripheral temperature. Several endpoints have been proposed, such as nasopharyngeal temperatures greater than 35.0 °C, bladder temperature greater than 36.2 °C [101] or skin temperatures greater than 30 °C [102]. We use an endpoint of 35.5 °C rectal temperature, which is supported by the literature [103]. Cardiac rhythm is carefully assessed, and if the desired sinus rhythm at an adequate rate has not been achieved, atrial and/or ventricular pacing are instituted. If arrhythmias occur that have the potential to compromise hemodynamic status after CPB, they are treated before separation with pharmacologic approaches or internal cardioversion.

Finally, blood gas values are measured before weaning from CPB to optimize electrolytes and Hct. Once the patient is ventilated, warm and in a stable rhythm, in addition to all the post-CPB requirements being met, weaning is initiated by slowly decreasing the venous return. Arterial perfusion is continued until the appropriate filling is reached. If all parameters are stable, modified ultrafiltration is started. The heart is observed carefully during this process to avoid overfilling or to recognize right heart failure early on. Also, radial artery pressure may not be accurate following CPB and tends to underestimate both the systolic and mean central aortic pressures. A questionable pressure should be confirmed with central aortic pressure measured from the aortic cannula. A pulse oximeter waveform appearing immediately after termination of CPB is a sign of good peripheral perfusion and adequate rewarming. There may be a larger arterial–alveolar gradient between end-tidal carbon dioxide and arterial carbon dioxide tension at the end of bypass due to ventilation-perfusion mismatch. A rapidly increasing area under the curve of the capnograph and increasing end-tidal CO_2 are signs of good cardiac output and the pulmonary status during the termination of CPB. TEE and/or epicardiac echocardiography are essential to evaluate the cardiac repair. TEE is used prior to separation to assist in de-airing the heart. After separation from bypass, it has become standard of care for most institutions and operations to evaluate heart function, assess the repair and any residual lesions prior to removing the cannulas. The recently published Residual Lesion Score (RLS) Study evaluated 1,149 infants undergoing five common procedures: tetralogy of Fallot, complete atrioventricular canal (CAVC), arterial switch, coarctation or arch interruption with ventricular septal defect (VSD), and Norwood stage I palliation [104]. RLS was assessed on postoperative echo and graded as 1 (trivial or no residual lesions), 2 (minor residual lesions), or 3 (major residual lesions with/without reintervention before discharge). RLS 3 was present in 15–35% of patients depending on the operation. Patients with RLS 3 for any lesion were significantly more likely to suffer adverse outcomes than RLS 1 (fewer days alive and out of hospital), and other major outcomes were worse with RLS3 for all lesions except TOF. (Total ventilation time, total ICU stay, major medical events including cardiac arrest, ECMO cannulation, neurologic event, and others) (Figure 11.9A). This important study emphasizes the importance of the immediate post-bypass TEE/epicardial echo, and the contributions of the entire intraoperative team to decision making about immediate reinstitution of bypass and revision of the surgical repair. See Chapter 15 for further details about TEE and epicardial echocardiography.

Conventional ultrafiltration and modified ultrafiltration

The application of the CPB machine in children leads to a significant capillary leak more often than is the case in adults. This is caused by the relatively larger foreign surface area exposure and the resulting greater inflammatory response.

Hemofiltration has been defined as ultrafiltration with the return of intravascular replacement fluids to compensate for losses. In contrast, ultrafiltration simply removes fluid through a convective process involving filtration across membranes. Conventional ultrafiltration (CUF) during CPB or modified ultrafiltration (MUF) after the end of bypass both

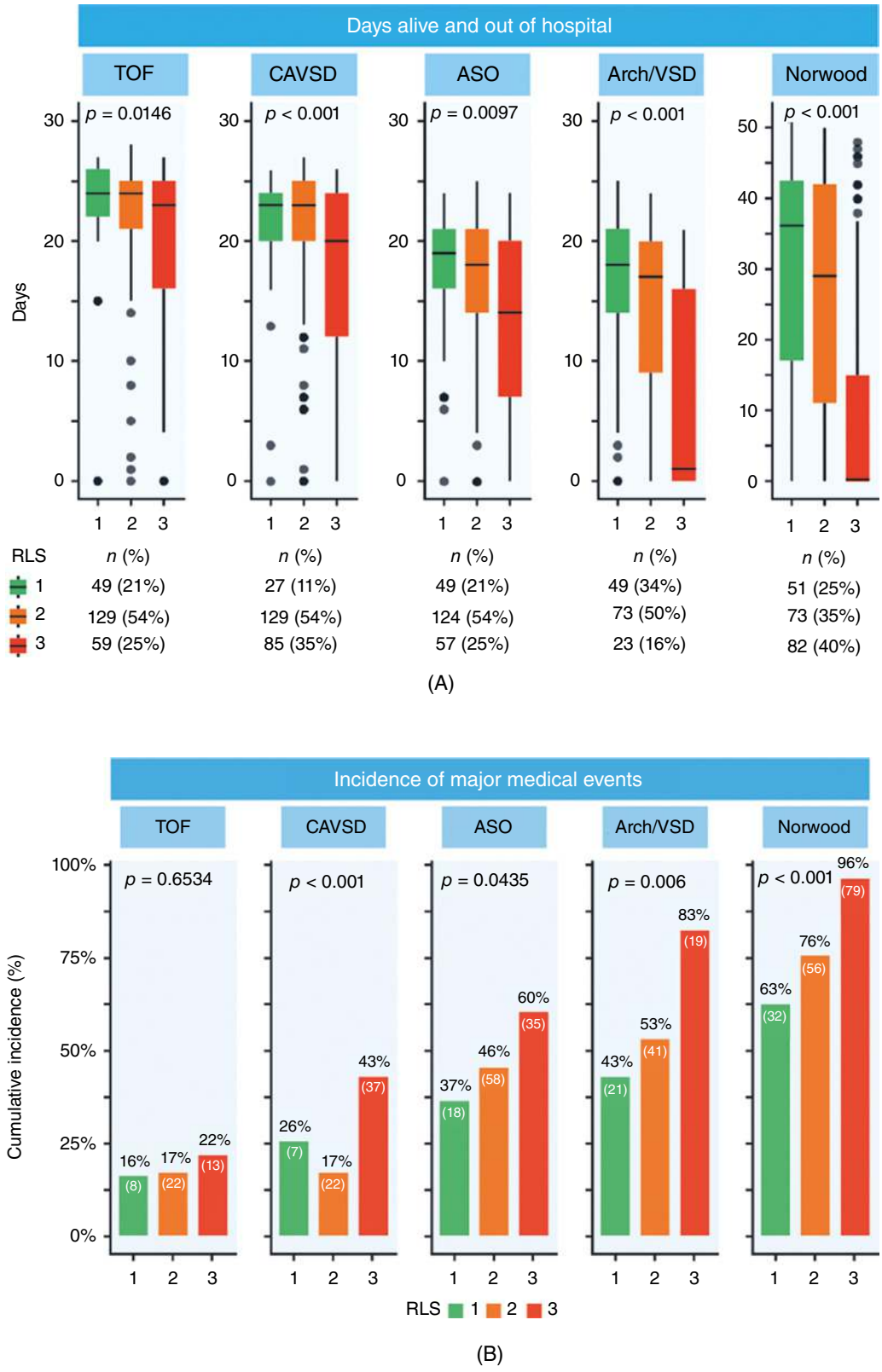


Figure 11.9 (A) Boxplot of days alive and out of hospital by RLS Score (higher number is better). The p values are from the Kruskal-Wallis Test. The number and percentage of patients in the 3 RLS classes are provided below the boxplot. TOF, tetralogy of Fallot; CAVSD, complete atrioventricular septal defect; ASO, arterial switch operation; Arch/VSD, aortic arch repair with ventricular septal defect; Norwood, Norwood stage I palliation. (B) Incidence of major medical events. P values are from Fisher's exact test. Includes mortality or heart transplant, cardiac arrest, ECMO cannulation, cardiac failure, mediastinitis, bleeding, neurologic event, renal failure, necrotizing enterocolitis, diaphragm or vocal cord paralysis, prolonged ventilation, sepsis, multisystem organ failure, noncardia operation, hemothorax, and readmission. (Source: Nathan et al. [104]. Reproduced with permission of Elsevier.)

reduce levels of proinflammatory cytokines and total interstitial body water after extracorporeal circulation. CUF and/or MUF are therefore standard procedures in all pediatric perfusion systems. The most commonly used procedure is MUF first described by Naik et al. [105, 106]. In this case, the bypass circuit is modified, and the flow is reversed at the end of CPB before protamine is given. Blood from the aortic cannula is directed through a hemofilter (blood flow rate of 100–300 mL/min) and infused back into the right atrium after warming and oxygenation. The ultrafilter pump is run at 10–30 mL/kg/min ultrafiltrate removal, with a vacuum on the ultrafilter. Replacement intravascular volume is infused from the venous reservoir as necessary. A steal phenomenon has been described whereby excessive flow rates divert blood from the aorta to the hemofilter, leading to cerebral and systemic deoxygenation. Several different methods of deciding when to terminate MUF are employed; some surgeons simply use a cutoff time of 15–20 minutes and others stop when the circuit volume has become diluted or when the desired Hct has been reached. Frequently, the surgeon's patience is the limiting factor. Filtering also will be stopped if the patient becomes hemodynamically unstable. Multiple beneficial effects can be observed (see Table 11.5); particularly important are the increase in Hct, the reduction of cytokines, improved myocardial perfusion, and a reduction in pulmonary vascular resistance (PVR) with the improvement of right heart function. Disadvantages of MUF are a delay in heparin reversal and decannulation of approximately 10–20 minutes, as well as the possibility of hemodynamic instability if preload is not adequately maintained by the perfusionist. However, surgical hemostasis can be carried out during this time period. The combination of MUF after CPB with zero balance conventional ultrafiltration (ZBUF) on bypass can eliminate additional unnecessary volume from cardioplegia or irrigation. The use of filtration during CPB (as conventional, dilutional, or zero balance ultrafiltration) also removes inflammatory mediators and vasoactive substances [107, 108]. Studies [109] have shown that compared with control patients, patients who have modified ultrafiltration after bypass have substantially less increase in total body water, have less interleukin-8 (IL-8) and complement in their bloodstream [110, 111], require less blood transfusion [112, 113], show improved coagulation factors [114, 115] and faster recovery of systolic blood pressure [105], pulmonary function [116], and cerebral metabolic activity [117] (Table 11.5). Modified ultrafiltration performed after CPB reverses hemodilution and decreases tissue edema and thereby accelerates postoperative recovery [118]. The combined use of ultrafiltration of prime solution, zero-balance ultrafiltration on bypass, and MUF strategy seems to be the most effective method, even though the principal clinical outcomes are similar between modalities [119]. A recent review of 90 clinical studies of the various forms of ultrafiltration concluded that MUF resulted in improved myocardial function, reduced fluid overload, and reduced bleeding and transfusion complications [120]. Zero-balance ultrafiltration (ZBUF) has been consistently associated with a reduction in inflammatory cytokines and improved pulmonary function and compliance. There is mixed evidence that any UF approach can reduce ventilation time and ICU stay. Because of the heterogeneity of the studies, no single approach was recommended.

Table 11.5 Effects of modified ultrafiltration

Parameter	Effect
PVR, PAP	Decreases due to oxygenation and warming
Stroke volume, CO	Left ventricular stroke volume increases secondary to improved pulmonary blood flow
SVR, blood pressure	Increases due to the reduction of vasoactive substances (interleukins, bradykinin, etc.)
Hemoglobin, hematocrit	Increases due to hemoconcentration
Interstitial body and lung water	Decreases secondary to water removal
Improved gas exchange [79]	Improved V/Q mismatch

Source: Elliott et al. [109]. Reproduced with permission of Elsevier.
CO, cardiac output; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SV, single ventricle; SVR, systemic vascular resistance; V/Q, ventilation-perfusion.

Failure to separate from CPB

Occasionally, despite escalating inotropic support, a child is unable to maintain adequate cardiac output and systemic oxygen delivery and therefore a return to CPB must be considered. An assessment of arterial blood gas and Ca^{2+} values, and whether intended inotropes are infusing correctly is important. Immediate TEE evaluation should be performed for the possibility of residual defects that require surgical attention. If no further surgical intervention is warranted, the source of the difficulty in weaning from CPB should be sought and other therapies must be considered. Is the Hct level adequate for this child? Too much hemodilution can lead to decreased systemic vascular resistance (SVR). The ideal Hct depends on the pathology and is probably in the range of 35–45% for complex repairs. Is the SVR too low? In children with low SVR who are either non-responsive to catecholamine infusions or who are experiencing adverse effects due to catecholamine therapy, arginine vasopressin has been shown to be a potent vasoconstrictor, with infusions resulting in increased MAPs and decreased catecholamine dependence. Its use in children appears promising when cardiac function is adequate [121, 122]. Fixed doses of 0.01–0.04 units/kg/hour of vasopressin are used. Exposure to endotoxin and cytokines as on CPB can trigger a *de novo* synthesis of the inducible, calcium-dependent isoform of nitric oxide synthase. Methylene blue inhibits this process by decreasing intracellular cyclic guanosine monophosphate concentrations through guanylate cyclase inhibition, thus blocking its vasodilator properties. It increases arterial pressure, SVR, and left ventricular stroke work, but does not increase cardiac output, oxygen delivery, or oxygen consumption. Methylene blue in a dose of 2 mg/kg followed by 1 mg/kg/hour has been used successfully in the setting of perioperative vasoplegia in adults [123], and neonatal sepsis [124], and in a case report of infective endocarditis in a 10-year-old girl [125]. Side-effects are rare in doses <2 mg/kg, but pulmonary hypertension and other side-effects can occur with repeat doses [126]. Is the right heart failing? Pulmonary hypertension

with resultant right heart failure may occur post-CPB, either as a result of long-standing increases in PA pressures or PVR, now exacerbated by the effects of CPB or as a result of acute increases in PA pressures or PVR secondary to protamine administration. Management has been challenging, as IV medications often affect both SVR and PVR. Selective pulmonary vasodilatation became possible with the introduction of inhaled nitric oxide (iNO), an endothelium-derived vasodilator that is rapidly deactivated by hemoglobin [127]. Several groups of patients have been shown to potentially benefit from iNO administration post-CPB [128, 129]. Patients with single-ventricle physiology undergoing total cavopulmonary anastomosis (Fontan procedure) with elevated PVR post-CPB, as well as children with elevated pulmonary venous pressures secondary to total anomalous pulmonary venous connection or congenital mitral stenosis, frequently show improvement with administration of iNO. For patients on iNO, caution should be exercised when transporting from the operating room to the ICU in order to avoid interruption of therapy, as rebound pulmonary hypertension and rapid clinical deterioration may occur. Other options to lower PVR include sildenafil 0.5 mg/kg through a nasogastric tube [130], IV sildenafil, or nebulized prostacyclin [131]. If severe left or right ventricular dysfunction persists in the absence of residual anatomic defects that can be surgically corrected, consideration may be given to continued mechanical support of the circulation. Currently, immediate pediatric options for mechanical circulatory support are extracorporeal membrane oxygenation or short-term left ventricular assist device in neonates, infants, and children. These techniques are most useful when recovery of ventricular function is expected within 24–72 hours, or when cardiopulmonary support is unavoidable. Cannulation configurations are shown in Figure 11.10 [132]. A recent review of postcardiotomy veno-arterial ECMO of more than 40 studies reporting more than 3,000 patients from 1990–2018 indicated a post-ECMO survival to hospital discharge of 40–60% in most studies [132]. Duration of ECMO support for survivors tended to be 3–5 days, and major complications included bleeding (13–69%), neurologic morbidity (11–51%), sepsis (10–50%), and renal failure (9–56%). Greater than 95% of reports of postcardiotomy mechanical support are ECMO. Veno-venous ECMO can be utilized for isolated respiratory failure. Another approach is short-term VAD support; Poh and colleagues reported 55 single ventricle patients supported with centrifugal VAD for postcardiotomy failure [133]. Median support was 3.5 days, and 53% were weaned off support, but only 33% survived hospital discharge. See Chapter 37 for further details about mechanical support.

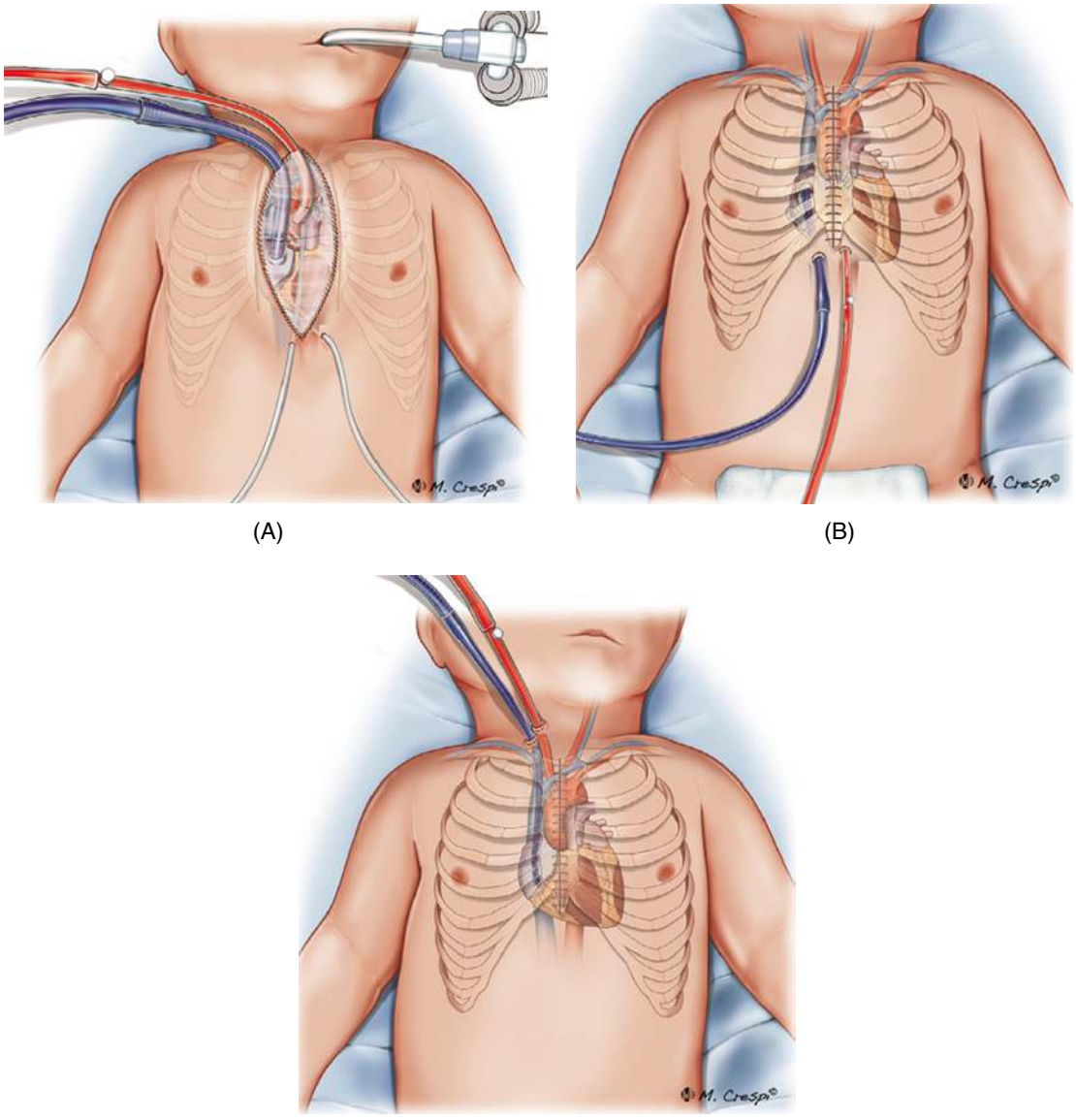
Heparin reversal and transfusion management

During modified ultrafiltration, cardiac function and the quality of the surgical repair are assessed via TEE, and if found to be satisfactory, protamine is administered to neutralize residual heparin after completing MUF. In small infants and palliated anatomies, the goal Hct separating from bypass should be 40–45%. This improves hemodynamic stability and allows immediate correction of coagulation disorders by infusion of blood products.

Protamine 1–1.5 mg/kg is given for each 100 units of the initial heparin dose to reverse its effect. This assumes that any further doses are given to maintain a heparin level and prevent overdosing of protamine with its associated effects on platelet function (reduction of the interaction of the glycoprotein Ib receptor with von Willebrand factor) [134]. If the ACT is still elevated or CPB prime (heparinized) blood is reinfused into the patient, an additional 25% of the initial dose of protamine is added and the ACT rechecked. However, particularly in infants, the administration of protamine and the persistent treatment of a suspected incomplete heparin reversal should not distract and delay the treatment of other commonly associated post-bypass coagulopathies such as thrombocytopenia, platelet dysfunction, and other coagulation factor deficiencies [135–138]. Individualized management of anticoagulation and its reversal results in less activation of the coagulation cascade, less fibrinolysis, and reduced blood loss and need for transfusions [58], while improving the clot stability as assessed by thromboelastography. However, care should be taken not to overdose the total amount of protamine [139, 140]. After one-third to one-half of the planned protamine dose is administered, blood from the surgical field must not be returned to the cardiotomy reservoir to avoid circuit thrombosis in case it is necessary to reinstitute bypass. An ACT or heparin level confirms adequate heparin neutralization. More protamine (0.5–1 mg/kg) can be given if either test remains prolonged and bleeding is a problem. Hypotensive protamine reactions can occur when protamine complexes with heparin because complement is released. This is much less common in children than in adults. Hypotension can be attenuated by adding calcium chloride (2 mg/mg protamine). Pediatric protamine reactions are rare, occurring in 1.7–2.8% of patients undergoing CPB [141]. Life-threatening reactions to protamine represent true allergic or pulmonary hypertensive reactions. Protamine reactions should be treated with epinephrine as the first-line agent and careful volume resuscitation as required. For severe reactions, it may be necessary to readminister heparin and resume CPB. Hemostatic management can be guided by thrombelastography. Newer devices allow a full "point-of-care" functional assessment of the coagulation within 10–15 minutes [142]. A recent retrospective study of 100 infants assessed before and after a heparin–protamine titration system (Hepcon®, Medtronic Corp. Minneapolis, MN, USA) reported that more limited protamine dosing neutralized heparin but also prevented anticoagulation effects (prolonged R values on thromboelastography [TEG]) caused by excessive protamine [139]. Further details can be found in Chapter 16.

Antifibrinolytic therapy

Bleeding is more common in pediatric cardiac surgery patients than in adults. Both qualitative and quantitative abnormalities in coagulation proteins have significant functional sequelae, which influence the hematologic responses to CPB. Cyanotic CHD itself is associated with coagulation abnormalities, including platelet abnormalities and fibrinolysis. There is extensive published research on the use of aprotinin and lysine analog antifibrinolytics to modify the adverse effects of CPB in adults, but for pediatrics, their dose and effects are much less clear.



(A) (B)

(C)

Figure 11.10 (A) Central ECMO cannulation via aorta and right atrium with the open sternum. (B) central cannulation via the aorta and right atrium with closed sternum and subxiphoid cannulae exit. (C) Peripheral ECMO cannulation via carotid artery and internal jugular vein with the closed sternum. Left atrial decompression may also be required with direct left atrial cannulation, atrial septostomy, or other methods. Also, if systemic to pulmonary artery shunt is present, it is usually partially occluded with a clip to limit pulmonary blood flow as in (A) and (B). (Source: Lorusso et al. [132]. Reproduced with permission of Elsevier.)

Two agents are currently available to modify the hemostatic response to CPB: ε-aminocaproic acid (EACA) and tranexamic acid (TA). Aprotinin, a serine protease inhibitor with anti-inflammatory properties, was withdrawn from the market in 2007 due to safety concerns in adult patients and will not be discussed further.

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA)

Both EACA and TA appear effective in reducing bleeding and transfusion in cyanotic patients, provided an adequate dose is administered. Their efficacy in other high-risk and mixed populations is not as well established. These drugs seem to lack significant clinical anti-inflammatory efficiency beyond their effects on coagulation [143, 144]. Suppression of excessive plasmin activity may play an important role in the generation of proinflammatory cytokines during and after CPB [145]. For an excellent and detailed recent review, please refer to Eaton [146].

Tranexamic acid dosing

Chauhan et al. [147], in a dose-ranging study of TA published in 2004, found the most effective dosing scheme of the four studied to be a 10 mg/kg load, 10 mg/kg in the pump prime,

and 10 mg/kg after protamine. More recent pharmacokinetic studies have shown effective concentrations of 20 µg/mL [148] using a dosing schedule with 6.4 mg/kg followed by 2–3.1 mg/kg, depending on weight [149]. Another pharmacokinetic-based scheme specifies for neonates 0–2 mo.: 15 mg/kg bolus; 20 mcg/mL of CPB prime; 2.5 mg/kg/hour infusion; for infants 2–12 mo.: 9 mg/kg bolus; 20 mcg/mL of CPB prime; 2 mg/kg/hour infusion; and children >12 mo.: 4 mg/kg bolus; 20 mcg/mL of CPB prime; 2 mg/kg/hour infusion [150]. Continuous and discontinuous doses of TA effectively inhibit fibrinolysis [151]. A high-dose regimen leading to blood concentrations greater than that required for D-dimer inhibition may be more efficient than lower dosages [152]. Previous studies have described TA doses of up to 100 mg/kg as a loading dose in infants and children; reports of seizures associated with high dose TA in adults combined with the pharmacokinetic data cited above argue against these doses and they should not be used in children. [153]

EACA dosing

Based on a pharmacokinetic study [154], in neonates, an initial loading dose of 40 mg/kg, an infusion of 30 mg/kg/hour, and a pump prime dose of 0.1 mg/mL of prime will maintain plasma concentrations above 50 mg/L in 90% of neonates. In older patients, the initial loading dose is 75 mg/kg, a pump-priming dose of 75 mg/kg followed by an infusion of 75 mg/kg/hour to establish and maintain a therapeutic plasma concentration (130 µg/mL) in 95% of patients [155].

Rapid IV injection of TA or EACA may cause hypotension. We infuse loading doses over approximately 20 minutes before the surgical incision. Some institutions delay antifibrinolytic dosing until the institution of bypass in patients who have systemic to pulmonary artery shunts, citing the risk of thrombosis.

Comparison studies of antifibrinolytics

With the considerable variability among studies of the three drugs under consideration in terms of design, dose, and outcomes, it is difficult to draw any conclusions about relative efficacy from the literature. There are a few published comparison studies. Chauhan et al. [156] compared low-dose aprotinin, EACA, and the combination in 300 cyanotic patients undergoing cardiac surgery. There was no difference between EACA-treated and aprotinin-treated patients in any measured variable. The same group compared TA and EACA in a placebo-controlled study of 150 patients with cyanotic CHD [147]. Both drugs were superior to placebo, but there were no significant differences between the treated groups with respect to 24 hours blood loss, transfusion, or re-exploration rate. Finally, the effects of aprotinin and TA were compared in 100 children, evenly divided into four groups: placebo, TA, aprotinin, and a combination of the two drugs [157]. Again, all treatment groups fared better than placebo in 24 hours blood loss and transfusion, with no significant differences among the three treated groups. Thus, the limited comparative evidence would suggest that the three drugs are equivalent in efficacy for reduction of bleeding and transfusion, at least with the doses and patients studied, and there is little or no advantage to combination therapy.

In summary, evidence supports the efficacy of the lysine analog antifibrinolytics EACA and TA, and aprotinin to decrease bleeding and transfusion in pediatric patients undergoing cardiac surgery involving CPB. This benefit is likely to be more significant in high-risk groups, such as cyanotic patients, newborns, complex surgeries, and reoperations. Aprotinin seems to have the strongest anti-inflammatory capacity of the antifibrinolytics [158]. The safety profile of these drugs is not fully understood, but each may have significant side effects that require further research in the future [159–161]. Further discussion of antifibrinolytic therapy is presented in Chapter 16.

KEY POINTS: MANAGEMENT OF PEDIATRIC CPB

- Pre-bypass, 300–400 units/kg heparin are injected to reach a target ACT >400 seconds.
- Two methods of cardioplegic arrest are used: hyperkalemic blood cardioplegia or hyponatremic crystalloid cardioplegia.
- Reperfusion after unclamping should be at least 8–10 minutes or 25% of the total cross-clamp time.
- Separation from bypass is initiated after the resumption of ventilation and reduction of venous outflow to fill the heart.
- Conventional ultrafiltration during CPB and modified ultrafiltration after CPB are commonly employed.
- Afterwards, heparin reversal is achieved with protamine, and coagulation disturbances are corrected with platelets and other coagulation products, guided by ACT and/or laboratory diagnostics (e.g., TEG).
- The antifibrinolytics TA and EACA are effective and used in most surgeries with an increased risk of bleeding.

Effects of CPB on organ systems

Cardiopulmonary bypass-induced systemic inflammatory response syndrome (SIRS) is a host response to the exposure of blood components to the foreign surface of the CPB circuit and initiation of the complement cascade. The early inflammation phase is triggered as soon as blood comes into contact with the synthetic circuit by activation of F-XII (coagulation factor) and C3 (immune factor) [162–164], and the late phase, following the release of the aortic cross-clamping, is driven by ischemia-reperfusion and endotoxemia. As a consequence, pro- and anti-inflammatory mediators are released into the circulation and the balance between these two groups of mediators is probably more important than the absolute levels of any of them [163–169]. Hypothermia and transfusion, frequently associated with pediatric CPB, are also two non-specific factors activating the inflammatory response [163–165, 167, 169–172]. Hypothermia modifies the metabolism of inflammation biomarkers by delaying, rather than decreasing, inflammatory systemic response [162–165, 167, 168, 173, 174]. Furthermore, genetic factors are involved in the inflammatory response and may

account for inter-patient variability [163–174]. Although the lungs are often the primary organ targeted, SIRS after CPB may be severe enough to affect other end-organ function. One of the major challenges is how to modulate the systemic inflammatory response, not only to control the drawbacks of inflammation but also to preserve a level of inflammation needed for host defense and wound healing. This should be the goal of further research.

Currently, there are a number of strategies being employed targeting the prevention of SIRS and multisystem organ failure, including the use of corticosteroids, protease inhibitors, thromboxane inhibitors or antagonists, prostacyclins, complement inhibitors, and cytokine inhibitors, including monoclonal antibodies and IL-1 receptor antagonist. With the exception of corticosteroids, all of these other approaches are experimental and thus far have not shown a beneficial effect on clinical outcomes, even though some have shown the intended effect on their molecular targets.

Multiple studies in children on corticosteroids have consistently shown a reduction in the inflammatory response, with some demonstrating improvement in clinical outcome [164–175]. A limiting factor in some studies using corticosteroids has been the lack of effect on clinical outcome and the higher incidence of postoperative infections and renal dysfunction with increasing cumulative corticosteroid exposure [166, 157, 170, 176–180]. The routine prophylactic use of steroids therefore cannot be recommended and may only be indicated in high-risk patients (DHCA, arterial switch operation) [176, 177]. A 2020 Cochrane review performed a meta-analysis of pooled data from eight randomized controlled trials in 478 patients [181]. Conclusions were as follows: (i) Moderate certainty of evidence that corticosteroids do not change the risk of in-hospital mortality (RR 0.83, 95% CI 0.33–2.07); (ii) high certainty that they do reduce the duration of mechanical ventilation (mean 11.39 hours lower, 95% CI 20.29–2.45). In addition, there was high certainty that corticosteroids made no difference in ICU stay, and moderate certainty of no difference in the hospital stay. The STRESS study is underway and will randomize 1,200 infants less than 1 year in multiple centers to methylprednisolone 30 mg/kg in the CPB prime vs. placebo in a blinded fashion [182]. Primary outcome is a global rank score of death, major morbidities, and hospital length of stay.

There is also evidence that pulsatile CPB flow significantly decreases endotoxin levels. An explanation could be the improved microcirculation and end-organ perfusion during pulsatile perfusion [178, 179]. However, there is a paucity of clinical studies demonstrating an outcome difference with this technique, and therefore, it has not been widely adopted in pediatric perfusion practice. For further details on the mechanism of end-organ dysfunction and treatment, refer to Chapter 12.

Neurological injury and protection

Brain injury in children with CHD has been documented before and after surgery for CHD. Some complications are apparent soon after the operation, such as seizures, stroke, and coma, whereas others appear long after the operation, such as cognitive deficits and psychomotor delay. Radiological and pathological studies have described a spectrum of brain lesions after pediatric cardiac surgery, located mainly in the neocortex, periventricular white matter, and basal ganglia, corresponding to the neurological deficits seen clinically [180, 183]. These subtle defects manifest as a developmental signature that includes cognitive and intellectual impairment, attention and executive function deficits, visual-spatial and visual-motor skill deficiencies, speech and language delays, and behavioral difficulties. The spectrum of lesions is consistent with hypoxic–ischemic injury, contrary to mostly embolic events in the adult population. When this injury occurs – before, during, or after the operation – remains uncertain. Adverse neurological outcomes after neonatal cardiac surgery are multifactorial and related to both fixed and modifiable mechanisms. Fixed factors include known genetic syndromes, structural central nervous system malformations (an incidence of up to 29% in HLHS) [183], multiple surgeries (leading to multiple insults), blood flow patterns *in utero*, preoperative cerebral hypoxia, embolic events occurring during the balloon atrial septostomy procedure [184], socioeconomic status, and a poorly defined genetic predisposition. Potentially modifiable factors include preoperative hypoxia–ischemia, intraoperative use of DHCA, neuroinflammation of the brain [185–187], and postoperative cardiopulmonary derangements [188]. Some interventions that may limit brain injury from DHCA include preoperative steroids, hyperoxygenation before DHCA, allowing at least 20 minutes of cooling to ensure adequate cerebral protection, packing the head in ice, intermittent cerebral perfusion between 15 and 20 minute periods of DHCA (Figure 11.11), and modified ultrafiltration after CPB. Other modifiable factors of CPB management include optimal flow at all temperatures [189, 190], the avoidance of extreme hemodilution [27] and emboli [191], pH-stat management [192, 193], and modulation of the inflammatory response by the use of ultrafiltration and steroids [164]. According to a recent meta-analysis, the only intervention supported by a high degree of evidence is the avoidance of extreme hemodilution to Hct below 25% [194]. Whereas myocardial protection and systemic oxygen delivery are continuously monitored during neonatal CPB, adequate cerebral perfusion has traditionally been evaluated by surrogate markers such as perfusion pressure, mixed venous oxygen saturation, or base deficit and lactate levels. However, there are now real-time intraoperative cerebral monitoring devices available for clinical use, the potential benefits of which are becoming recognized [195]. The most widely used technologies include NIRS, transcranial Doppler, raw and processed electroencephalography, and serum measurement of S100B protein. Real-time technologies allow immediate interventions upon interruption of optimal cerebral flow and may improve outcome [196]. Improved strategies to prevent injury in these arenas are much needed [197]. For an extensive discussion of neurological monitoring and outcomes, see Chapter 14.

Pulmonary effects

Post-bypass lung injury may be a result of ischemia-reperfusion injury or may be associated with the systemic inflammatory response caused by extracorporeal circulation [198]. Alveolar injury is also associated with cyclic closing and opening of alveoli, with shear injury to the

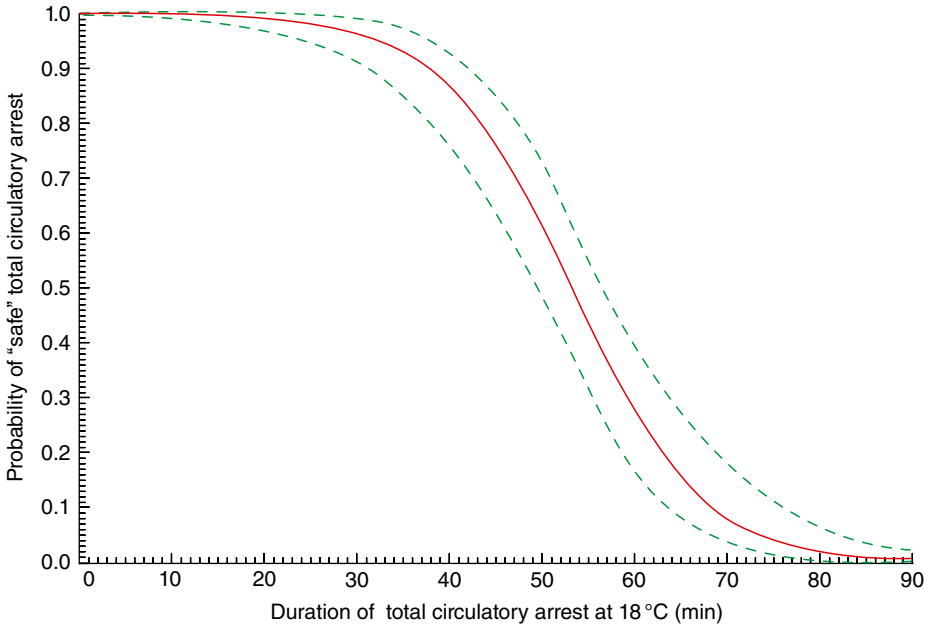


Figure 11.11 Probability of "safe" deep hypothermic circulatory arrest. At 18 °C, the likelihood of neurological injury becomes exponentially greater beyond 45 minutes of circulatory arrest. (Source: Kirklin and Barrett-Boyes [68]. Reproduced with permission of Elsevier.)

alveolar-capillary interface causing increased permeability and pulmonary edema with a significant pulmonary inflammatory reaction [199]. Etiologies of postoperative pulmonary dysfunction after CPB include a decrease in total lung capacity, functional residual capacity, atelectasis, pulmonary edema, increased inspiratory oxygen, and ventilation-perfusion mismatch [200]. Administration of a FiO_2 of 1.0 during CPB may lead to absorption atelectasis and oxygen toxicity. Lung injury could be prevented in a piglet model using continuous pulmonary perfusion on CPB [201]. In a study by Pizov et al. [202], lung function improved later postoperatively in patients ventilated with 100% oxygen during CPB. Several studies have assessed modes of ventilation on bypass and their effects. Continued ventilation throughout CPB is associated with superior postoperative respiratory function in certain clinical scenarios, possibly due to attenuation of the ischemia–reperfusion injury, but this technique has yet to gain wider acceptance. Maintaining ventilation and PA perfusion during CPB has shown some benefits in limiting pulmonary platelet and neutrophil sequestration, and attenuating thromboxane B_2 response after CPB [203, 204]. To date, the evidence favoring continuous ventilation alone during CPB on cardiopulmonary function is inconsistent, with most studies showing no benefit [205–207]. At our institution, we prefer continued ventilation at low tidal volumes, room air, and low positive end-expiratory pressure (PEEP) settings in patients undergoing simple procedures without cross-clamping like a right ventricle–conduit exchange, etc. if tolerated by the surgeon. Many surgeons will require total lung collapse to allow complete access to the heart, without movement, for neonatal and infant patients with limited intrapericardial space. In more complex cases, we start ventilation after thorough pulmonary toilet and suctioning with a recruitment maneuver. This is usually done in the context of de-airing and aortic clamp removal. Afterward, we continue ventilation at low settings with approximately 2 mL/kg and a PEEP setting of 5–8 cm H_2O with a FiO_2 of 0.21. Full ventilation is resumed just before weaning from bypass, usually in a pressure-regulated, volume-controlled mode to maintain minute ventilation with stable tidal volumes. The pressure limit is carefully monitored and set 5 cmH_2O above the upper inspiratory pressure.

Renal, hepatic, and gastrointestinal effects

Little is known about the epidemiology and risk factors for the development of acute renal failure in children post-CPB for cardiac surgery. The incidence of acute renal dysfunction complicating open-heart surgery in children is significant, at 11–17% [208, 209]. Low cardiac output was a significant predictor of developing a renal injury. Other risk factors include young age, the preoperative need for mechanical ventilation, use of milrinone, gentamicin and furosemide, the duration of CPB and anesthesia and multiple cross-clamp times as well as the transfusion of blood products [210]. This is often related to the complexity of the operation. Unexpectedly, DHCA was not a predictor of postoperative renal dysfunction. On the one hand, better and more sophisticated surgical and CPB techniques are available, while on the other, children with more complicated cardiac lesions requiring longer CPB time are operated on today. There is also evidence that the neonatal kidney is more vulnerable to conditions of hemodynamic stress [209] with loss of autoregulation leading to blood pressure-dependent renal blood flow and ischemia-induced renal injury. All of these conditions render the neonate more prone to complications of ischemia than the older infant or child. Renal replacement therapy is required in 1.6–7.7% of patients. In children, the mortality rate in those requiring dialysis following CPB is reported to

range from 46 to 67%. However, renal failure is often temporary. Among those who recover, 93–100% of survivors of renal replacement therapy after CPB surgery have normal renal function at discharge from the hospital [211, 212]. Peritoneal dialysis (PD) is a safe and effective treatment for children after CPB surgery and should be initiated early in the course of acute renal injury [213–217]. Peritoneal dialysis is also utilized in some centers routinely after complex neonatal and infant surgery, to counteract the frequent low urine production from antidiuretic hormone release and acute renal ischemic effects [215]. Peritoneal dialysis also effectively filters inflammatory mediators, and the overall result is to limit fluid accumulation and shorten the time of mechanical ventilation [218]. Kwiatkowski and colleagues randomized 73 patients <6 months who had oliguria after CPB surgery to PD vs. furosemide for prevention of fluid overload [219]. The furosemide group had a three-fold higher risk of 10% fluid overload and was more likely to have prolonged ventilator and inotrope use, and higher electrolyte abnormality scores. There were no differences in mortality, or ICU or hospital stay. There were no serious complications of PD. Plasma and urine neutrophil gelatinase-associated lipocalin thresholds are early predictive biomarkers for AKI [220]. A recent review of AKI after CPB in infants reinforces the conclusions noted above; despite some promising research on biomarkers of renal injury, none has become clinically available; the principles of supporting cardiac output and instituting renal replacement therapy early when AKI is recognized are emphasized [221].

Several investigations provide evidence that intestinal organ function is altered during CPB. Splanchnic, but not systemic, oxygen extraction increases during normothermic, non-pulsatile CPB. Splanchnic blood flow is not significantly affected by normothermic or hypothermic CPB at normal pump flows compared with the pre-bypass condition [222, 223]. The increase in splanchnic oxygen extraction during hypothermia, indicating a splanchnic oxygen supply/demand mismatch, was, therefore, most likely caused by a decrease in splanchnic oxygen delivery, in turn, caused by a decrease in hemoglobin concentration secondary to hemodilution. The splanchnic region might be more susceptible to a decrease in oxygen delivery by hemodilution, compared with other organs. Normothermic CPB leads to a loss of gastrointestinal (GI) barrier function independent of the duration of CPB. Current data indicate that intestinal mucosal autoregulation is maintained during CPB within the pressure range 50–75 mmHg [224]. Improving pump flow rather than infusing vasoconstrictive drugs to increase aortic pressure can improve both splanchnic and renal perfusion [225], and improve the postoperative course in children [226]. Although GI complications may have a low incidence (0.3–3%), they are associated with high mortality (13–63%) [227, 228]. Several risk factors (e.g., use of vasopressors, pre-existing comorbidities, perioperative hypotensive episodes, and valve surgery) have been evaluated for the development of alterations in GI organ function. Liver dysfunction rarely occurs after CPB.

Endocrine and metabolic response to CPB

In children, hypoalbuminemia and hyperchloremia are the predominant acid-base abnormalities after CPB, whereas lactic acidosis and wide ion gap acidosis are rare [229]. Hyperchloremia following CPB appears to be a benign phenomenon. By contrast, hypoalbuminemia, an alkalinizing force, was associated with a prolonged requirement for intensive care.

KEY POINTS: EFFECTS OF CPB ON ORGAN SYSTEMS

- A SIRS is the natural response of the body to contact with the circuit, surgery, and the disturbance of homeostasis.
- Multiple interventions have been attempted with minimal success except for the avoidance of blood transfusion and the minimization of the contact surface.
- All major organs are affected, from neuroinflammation to acute lung, GI tract, and kidney injury, as well as metabolic and endocrine disturbances.

Special CPB management issues

Warm CPB

Hypothermic CPB associated with cold myocardial protection is commonly used for neonatal cardiac surgery. The rationale is to protect the brain in case of failure of oxygen delivery (Figure 11.12). In addition, hypothermic bypass helps to complete cold myocardial protection by delaying myocardial rewarming and maintaining a low metabolic state. There is a growing body of evidence demonstrating that hypothermia also induces deleterious effects, which may culminate in end-organ dysfunction. The benefits of hypothermia are balanced by its drawbacks, including impaired hemostasis [230], microcirculatory dysfunction, capillary leakage, endotoxin release, disturbed glucose metabolism [231], and decreased myocardial contractility [232]. Hypothermia delays the recovery of the mechanical function of the myocardium and reduces basal metabolism.

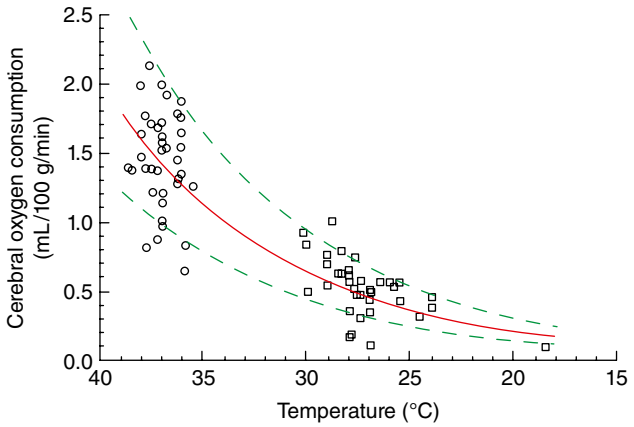


Figure 11.12 Relationship between cerebral oxygen consumption and nasopharyngeal temperature during bypass at a flow of 2 L/min/m². (Source: Kirklin and Barrett-Boyes [68]. Reproduced with permission of Elsevier.)

This reduction has only a minimal impact on oxygen needs. Less well understood is the deleterious effect of hypothermia on the myocardium. Reactivity of the microcirculation is impaired after deep hypothermia, as are many cellular functions. The lungs are very sensitive to CPB, and hypothermia may increase the capillary leakage more than normothermia by inducing microcirculatory dysfunction and impairing endothelial responses [233]. By reducing oxygen demand, hypothermia is effective in protecting the brain, but it impairs vasomotor and cerebral oxygen regulation [234], alters energy metabolism [235], and increases intracranial pressure, and overshoot during rewarming may induce neurological injury [236]. Furthermore, the protective effect of hypothermia on the inflammatory reaction and neurological recovery may have been previously overestimated [237]. The inflammatory reaction induced by CPB seems to be delayed rather than diminished by hypothermia [238]. Finally, with prolonged DHCA, long-term follow-up has shown impaired neurodevelopmental outcomes [239]. Therefore, normothermic CPB, already commonly used in adult cardiac surgery, has been promoted and progressively extended into pediatric practice [240]. Favorable surgical results have been achieved with normothermic bypass for even complex operations such as the arterial switch operation [241]. See the section above under Cooling and Temperature Management for more details.

Temperature is not the only characteristic of normothermic CPB. Other factors to be considered are flow and Hct. The flow generally used for mild hypothermic CPB is 2.0–2.4 L/min/m^2 (Figure 11.8). In normothermic CPB, pump flow is maintained throughout the procedure at 3.0–3.5 L/min/m^2. In terms of hemodilution on CPB, Hct is maintained above 30% during the procedure, with 40% by the end of CPB for normothermic CPB. Thus, normothermic CPB is better characterized by "normothermic, high-flow, high- hematocrit CPB" [57].

Deep hypothermic circulatory arrest

Hypothermia has been utilized since the early days of CPB to allow reduced flows in order to improve intracardiac surgical exposure. Bigelow et al. were the first to demonstrate in 1950 that hypothermia decreases the metabolic rate [242] (Figure 11.12). It decreases blood loss [240], provides myocardial protection [243], and, most importantly, is neuroprotective [244]. This mostly relates to the decrease in the metabolic rate by 64%, by cooling from 37 to 27 °C. Also, at a given temperature, the amount of gas in the solution increases proportionally to the decrease in temperature (ideal gas law). In CPB, this translates to cooling the patient not only to lower the metabolic rate but also to obtain a higher solubility of oxygen in blood and tissues. Pearl et al. [245] were able to show that the use of hyperoxia with a pH strategy led to the lowest production of acids during 60 minutes of DHCA. This is probably related to increased tissue oxygen loading pre-arrest.

The disadvantages of hypothermia include disruption of cerebral autoregulation (Figure 11.13) prolongation of CPB, and a greater tendency toward postoperative bleeding [246]. Postoperative recovery, however, is not prolonged by hypothermia [247]. Also, the wound infection rate does not seem

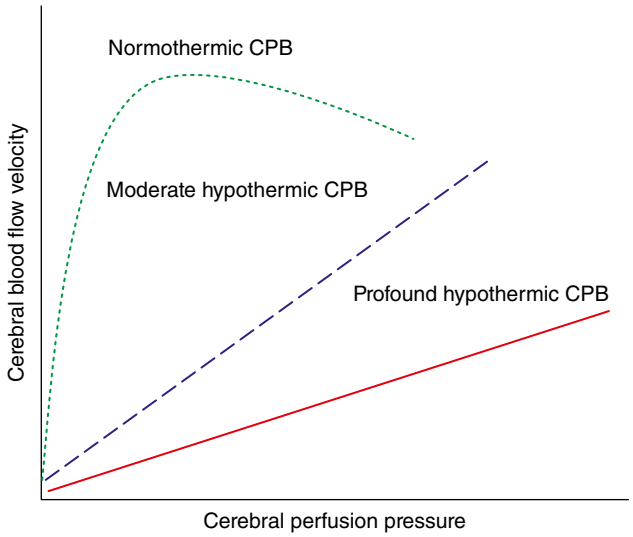


Figure 11.13 Cerebral blood flow velocity vs. cerebral perfusion pressure at different bypass temperatures. During normothermia, a normal pressure-flow velocity relationship is observed; during moderate or profound hypothermia, autoregulation is affected, and blood flow velocity is proportional to cerebral perfusion pressure in a linear relationship. (Source: Hillier et al. [234]. Reproduced with permission of Wolters Kluwer Health, Inc.)

to be influenced by hypothermic bypass [248]. Hypothermia during cardiac surgery only gained widespread use after the development of a heat exchanger that could be integrated into the CPB machine [249].

Deep hypothermic circulatory arrest involves cooling the patient's body temperature to 17–18 °C, stopping the bypass machine, draining the blood from the patient into the venous reservoir, and removing the cannulas from the heart. After the first reports of DHCA in the 1960s, this technique gained popularity in the 1970s and 1980s, because of the perfectly bloodless field it provided. This facilitated complex intracardiac and aortic repairs in newborns and small infants [250], as well as reducing edema. However, it soon became evident that DHCA was associated with neurological morbidity. Choreoathetosis, seizures, coma, and hemiparesis were all noted, especially with prolonged DHCA (>60 minutes) [251]. Clinical and experimental evidence suggests that DHCA preferentially damages the basal ganglia, which control tone and movement. The main input of the basal ganglia is the striatum, a highly dopaminergic region of the brain. Increases in free dopamine levels as an indicator of brain damage and cell disruption occur earlier in prolonged DHCA than in low-flow bypass strategies [252], and about 15 minutes earlier using alpha-stat versus pH-stat management [253]. It is interesting to note that the incidence of these acute morbidities seemed to increase when alpha-stat management became the accepted standard in many centers. Long-term adverse neurodevelopmental outcomes have also been associated with long periods of DHCA, including abnormalities in mental development [194], and in fine and gross motor skills. The Boston Circulatory Arrest Study is a remarkable achievement in which 180 newborns undergoing the arterial switch operation from 1988 to 1992 were studied, with follow-up now complete to the age of 16 years [254, 255]. The CPB

protocol in those years included alpha-stat management, routine hemodilution to a Hct of 20%, and the absence of an arterial filter on the CPB circuit. A DHCA time of greater than 41 minutes was associated with a significant increase in long-term neurodevelopmental problems. The effect of longer DHCA times was diminished, although still present at age 16 years with an association with lower visual-spatial scores and executive functioning. In the same patient cohort at age 16 years, shorter cooling time and higher nadir temperature were associated with impaired microstructural development of deep subcortical white matter when assessed with quantitative magnetic resonance imaging (MRI) [256]. In a recent study from a cohort of neonates undergoing surgery from 2004 to 2008, a longer duration of DHCA was also associated with a higher incidence of white matter injury on postoperative MRI [257].

Although the 41 minute cutoff is now a well-accepted limit in congenital heart surgery, multiple changes have subsequently been made to bypass protocols. Results from animal experiments utilizing a neonatal piglet model of DHCA, as well as data from the Boston Circulatory Arrest Study, led to the following recommendations for increasing the patient's safety margin when utilizing DHCA:

- Hematocrit of 25–30% should be the target [258].
- Systemic hypothermia should be achieved slowly, over no less than 20 minutes (Figure 11.14).
- pH-stat blood gas management should be used, at least for cooling, to improve tissue oxygen loading and more even cerebral cooling (Figure 11.15) [259, 260]. Core body temperatures of 17–18 °C should be utilized, and ice bags should be applied to the head [261]. Hyperoxia immediately before DHCA improves tissue oxygen loading [247].
- DHCA should be divided into periods of no longer than 20–30 minutes, allowing a reperfusion period of at least 2 minutes between each segment of DHCA, to improve neurological outcome [262].

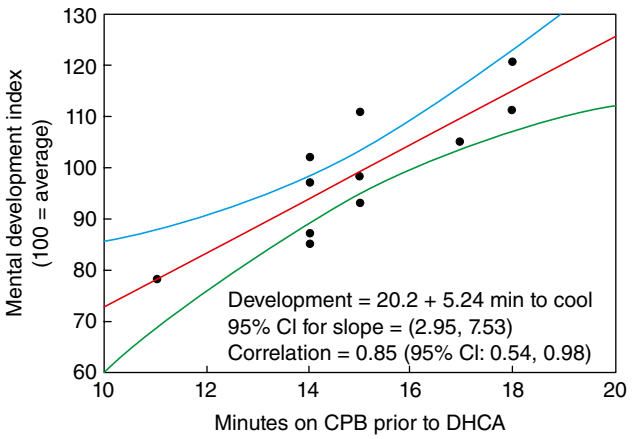


Figure 11.14 Cognitive development following neonatal repair of transposition of the great arteries using deep hypothermic circulatory arrest (DHCA) at 18 °C. Minutes on cardiopulmonary bypass (CPB) prior to DHCA = cooling time. Cooling times <20 minutes were associated with lower neurodevelopmental outcome scores at age 12 months. CI, confidence interval. (Source: Bellinger et al. [69]. Reproduced with permission of American Academy Of Pediatrics.)

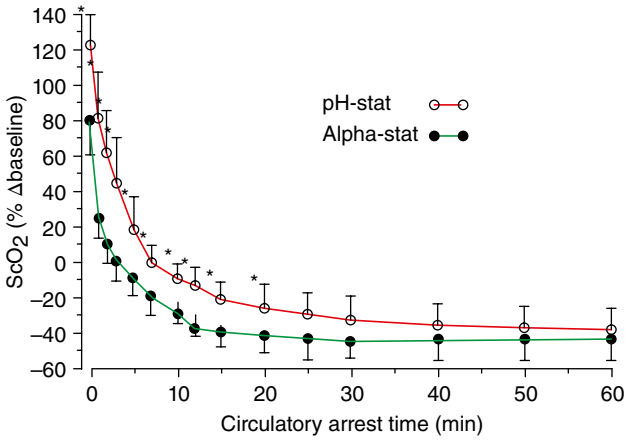


Figure 11.15 Decline in cerebral oxygen saturation (ScO_2) during deep hypothermic circulatory arrest in piglets. pH-stat management resulted in higher ScO_2 during the first 20 minutes of circulatory arrest. (Source: Kurth et al. [259]. Reproduced with permission of Wolters Kluwer Health, Inc.)

- Low-flow CPB (at greater than 40–50 mL/kg/min) offers greater cerebral protection than DHCA [263]; regional cerebral perfusion may be better than low-flow CPB (see later).
- Cold normoxemic reperfusion of the brain after DHCA for 5–10 minutes may be beneficial to restore cerebral autoregulation and wash out accumulated metabolites before adding the metabolic burden of rewarming to the brain [264]. Controlled reoxygenation was also associated with reduced myocardial damage, oxidative stress, and cerebral and hepatic injury in cyanotic children despite similar inflammatory responses to hyperoxia [265].
- Normoxemia should be maintained to decrease exacerbation of brain injury after DHCA [266]. Neurological monitoring is useful in the individual patient to aid in determining the safe duration of DHCA [259, 267] (Figure 11.5).

Although there are situations where DHCA must be utilized, many surgeons are avoiding it whenever possible, by minimizing its duration and dividing the periods of its use, or using alternative methods, such as regional cerebral perfusion.

In the current era, DHCA is used by some surgeons for the following indications:

- Surgery for interrupted aortic arch
- Stage 1 palliation for hypoplastic left heart syndrome (HLHS)
- Obstructed total anomalous pulmonary venous drainage (TAPVD) (especially with a small pulmonary venous confluence)
- Repeat surgery for recurrent pulmonary vein obstruction in TAPVD
- Surgery on low-birth-weight neonates <2 kg

Regional cerebral perfusion

In order to avoid the use of DHCA, several novel CPB techniques have been developed over the past 15–20 years to allow perfusion of only the brain during critical periods of surgery, such as aortic reconstruction during the Norwood

operation, interrupted aortic arch repair with ventral septal defect (VSD), coarctation with VSD, or cases requiring the Damus–Kaye–Stansel procedure [268, 269]. These techniques are collectively referred to as regional cerebral perfusion (RCP). Other terms for this technique are regional low-flow cerebral perfusion, selective cerebral perfusion, antegrade cerebral perfusion, and selective regional cerebral perfusion. Several different techniques have been described on the basis of the primary description by Pigula et al. [268]. One variation of RCP utilizes a small Goretex graft of 3–4 mm sewn onto the innominate artery prior at the initiation of CPB, and this is then used as the aortic cannula during CPB. A pre-CPB test occlusion by the surgeon of the innominate artery with bilateral rSO_2 monitoring can serve as a functional test of an intact circle of Willis. If there is a significant and reproducible decline in rSO_2 on the side of the innominate occlusion, a non-intact circle of Willis (up to 5% of neonates) is assumed and a different CPB strategy (i.e., DHCA) can be planned. Other options for cannulation include a high cannulation technique of the innominate artery with a small 6 or 8 Fr. aortic cannula, which is advanced cephalad further distal into the innominate artery during RCP [270] (Figure 11.16). During aortic reconstruction, snares are placed around the brachiocephalic vessels and CPB flow is decreased, with only the brain receiving perfusion via the right carotid artery during this period. In this way, a bloodless operative field can be achieved, just as if DHCA was being performed, yet the brain

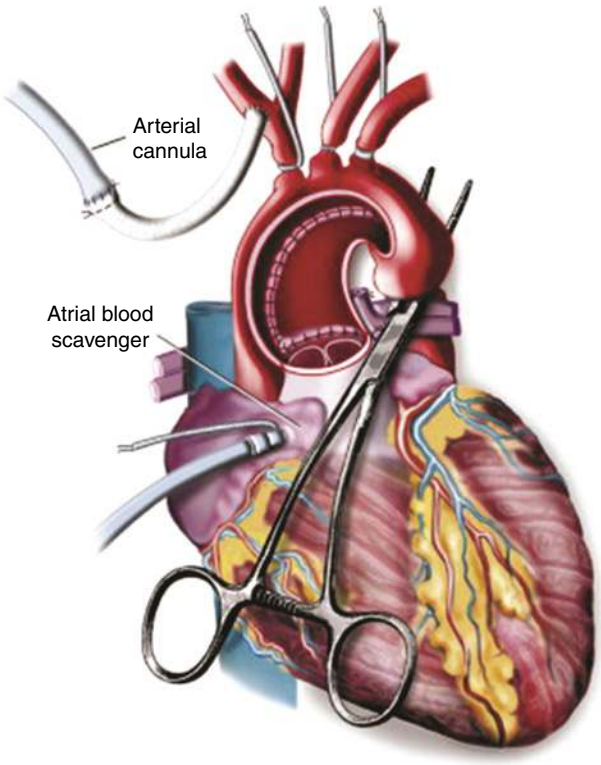


Figure 11.16 Regional cerebral perfusion during aortic arch reconstruction for hypoplastic left heart syndrome. A polytetrafluoroethylene graft is sewn to the right innominate artery as the aortic cannula inflow. Brachiocephalic vessels and descending aorta are snared, and perfusion to the brain occurs, leaving a bloodless operative field. (Source: Pigula et al. [268]. Reproduced with permission of Elsevier.)

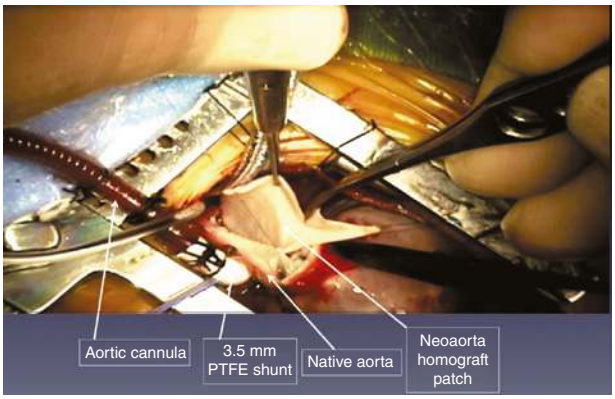


Figure 11.17 Regional cerebral perfusion. Note the bloodless operative field and the position of the graft and cannula.

is still receiving blood flow and oxygen, in theory increasing protection from hypoxic-ischemic brain injury (Figure 11.17). Another potential advantage of this technique is seen in newborns who have extensive arterial collaterals between the proximal branches of the aorta and the lower body via the internal mammary and long thoracic arteries. In this instance, the use of RCP also provides some blood flow to the lower body, potentially protecting renal, hepatic, and GI systems from ischemic damage as well [232, 271, 272]. Preliminary results are promising and support the notion of improved cerebral protection [270, 273], even at mild hypothermic temperatures [272, 274]. Neurological monitoring has been used to aid in determining how much flow is necessary during RCP [275]. Approximately 40–50% of full flow is used (starting at 40 mL/kg/min) and adjusted according to brain saturation and/or transcranial Doppler measurements, maintaining baseline saturation in the range before the onset of RCP (90–95% range). Average flows of 50–65 mL/kg/min during RCP are required to maintain baseline cerebral blood flow velocities, rSO_2, and pressures to overcome vessel resistances and capillary opening pressures [273, 276]. Flows <40 mL/kg/min over time are unable to maintain rSO_2 greater than 40% after DHCA [277]. If the left regional saturation rSO_2 falls to more than 10% below the right, flow is increased further, assuming that the circle of Willis could be variant or incomplete, as all flow to the left cerebral hemisphere needs to traverse the circle. If a left radial arterial line or a femoral arterial line/umbilical artery catheter is in place, abdominal perfusion pressures of >12 mmHg, correlating to radial artery pressures of 25–30 mmHg, are maintained [271].

Despite these theoretical advantages, and a study demonstrating that selective cerebral perfusion does provide oxygenated blood flow to both cerebral hemispheres [273], longer-term neurodevelopmental outcome studies to date have not demonstrated clear superiority of RCP vs. DHCA for aortic arch reconstruction in neonates. Andropoulos et al. reported 12 month neurodevelopmental outcomes of a cohort of 34 neonates after RCP using the Bayley Scales of Infant Development III and found the mean cognitive score equal to the reference population norm, while the language and motor scores were both 0.8 standard deviations below norms [278]. Later outcomes at 3 years of age after RCP in this cohort revealed Cognitive, Language, and Motor scores averaging

95 (0.33 standard deviation below norms). At 5 years, when more comprehensive testing is possible, IQ domains and language scores averaged 97–98; motor skills 90, and visual-motor integration 92 [31]. The study was not controlled and used the newest version of the Bayley test, preventing direct comparison with earlier studies by Goldberg (57 patients) [279] and Visconti (29 patients) [280], which demonstrated no neurodevelopmental outcome difference between RCP and DHCA, with both mental and motor scores significantly lower than population norms at 12 months. Algra et al. [281] randomized 36 HLHS patients undergoing Norwood stage I operation to DHCA vs. RCP and performed postoperative brain MRI. The overall incidence of new brain injury was significant at 76% and not different between groups, although the RCP patients were the only ones with new infarctions in deep brain structures. Significantly, RCP flow rates were higher in the Andropoulos et al. study [278] than in the other three, and theirs was also the only one to employ neurological monitoring to adjust RCP flows. Xie and colleagues reported a retrospective study of two ventricle infants undergoing aortic arch repair with DHCA at 18–20 °C ($n = 53$) compared to RCP at moderate hypothermia at 25 °C [282]. The RCP group had a lower rate of acute neurologic complications 3/61 vs. 10/53, $p < 0.05$), and a shorter duration of mechanical ventilation and ICU stay. Hoffman and colleagues reported long-term neurodevelopmental outcomes of 178 neonates followed out to 36 months of age [283]. Furthermore, 51 were single ventricle patients employing an RCP protocol with neuromonitoring and higher flows. Cognitive scores averaged 100, Language 95, and Motor 101 on the Bayley III, and were not different from the two-ventricle patients. Outcome studies of RCP must be interpreted with caution and the details of the technique must be assessed [273–283]. The differences in the various neurodevelopmental tests as new versions are developed also need to be taken into account [284]. The two studies employing neuromonitoring and higher RCP flows [31, 283] report neurodevelopmental outcome studies with most domains in the normal range at 3–5 years, in contrast to studies with lower flows and no neuromonitoring.

Alternative cannulation strategies for neonatal aortic arch reconstruction have been described to provide perfusion to the brain as in RCP, but utilize one or two additional cannulae to perfuse the descending aorta and subdiaphragmatic viscera, and aortic root to perfuse the myocardium while allowing a bloodless field [285–287]. In these studies, operating time was reduced, postoperative serum lactate concentrations were lower and fewer days were required for sternal closure. Kulyabin and colleagues randomized 15 infants undergoing aortic arch reconstruction to DHCA at 18–20 °C, RCP at 23–25 °C, and flows of 30–50 ml/kg/min, or RCP plus descending aorta cannulation at 28–30 °C [288]. Mortality was not different between groups, although 5 patients died early postoperatively. The risk of new postoperative MRI findings was higher in the DHCA group; 12/15 vs. 5/15 in both of the other groups ($p = 0.019$). The composite of all unfavorable events was lower in the RCP plus descending aorta cannulation group ($p = 0.041$).

In summary, there is no prospective, randomized controlled published evidence that demonstrates the superiority of any of these cannulation or bypass techniques in terms of quality of surgical reconstruction and hospital mortality. Since the Boston Circulatory Arrest Trial there has been a definite trend toward employing continuous CPB and minimizing DHCA for most pediatric cardiac procedures.

Blood gas management: pH-stat vs. alpha-stat

Some degree of hypothermia is utilized for nearly every cardiac operation in order to slow the metabolism and oxygen consumption of all organs, particularly the brain and heart [289]. During cooling, the carbon dioxide contained in blood becomes more soluble and its partial pressure decreases. The $PaCO_2$ sensed by the body therefore decreases as body temperature decreases, with the result that at a core temperature of 17–18 °C, if pH and $PaCO_2$ have not been corrected for temperature, the body is experiencing a pH of about 7.6 and $PaCO_2$ of 15–18 mmHg [290] (Figure 11.18). This very low $PaCO_2$ causes cerebral vasoconstriction, particularly during the cooling phase of bypass, which in turn leads to lower cerebral blood flow, less efficient brain cooling, and consequently less cerebral protection at a given temperature [259]. Since blood samples are heated to 37 °C prior to measurement of pH, $PaCO_2$, and PaO_2, the use of pH-stat management necessitates that blood gases are being corrected for the patient's actual body temperature by increasing the $PaCO_2$ on bypass as it is measured at 37 °C, so that the body experiences a $PaCO_2$ of approximately 40 and a pH of 7.4 at all temperatures. Conversely, alpha-stat management means not correcting the blood gases for temperature, as if the patient's blood was always at 37 °C, with the goal of a pH of 7.4 and $PaCO_2$ of 40 mmHg. In the early history of CPB, pH-stat was utilized to preserve cerebral blood flow [291]. Randomized controlled studies in the 1970s and 1980s on adults undergoing CPB confirmed that acute, post-CPB neurological problems were worsened with the use of pH-stat management [292]. Alpha-stat management was, therefore, adopted for both adult and pediatric CPB. However, recent animal studies in a neonatal piglet model have challenged this conclusion, proving that neurological outcome, both behavioral and neuropathological, is significantly worse when alpha-stat management is used [259, 260].

Advantages of pH-stat CPB have been shown to include:

- a decreased brain metabolic rate
- an increased rate of brain cooling and reperfusion [293], thereby providing better protection through more even and faster cooling and rewarming secondary to increased CBF [293, 294].
- molecular effects of altered arterial PO_2 and pH, including changes in cerebral oxygenation and brain enzyme activity as well as decreased brain electrical activity [295–296].
- improved oxygen delivery through decreased oxyhemoglobin affinity [297] by counteracting the pH and hypothermia-associated leftward shift in the oxyhemoglobin dissociation curve
- increased cortical oxygenation before arrest (through hypercapnic capillary vasodilation [298]) and decreased oxygen metabolic rate providing slower deoxygenation compared to alpha-stat management (10 vs. 7 minutes) [259] (Figure 11.15). Cortical anoxia occurs at 36 vs. 24 minutes for alpha-stat management, a safety margin of 50%.

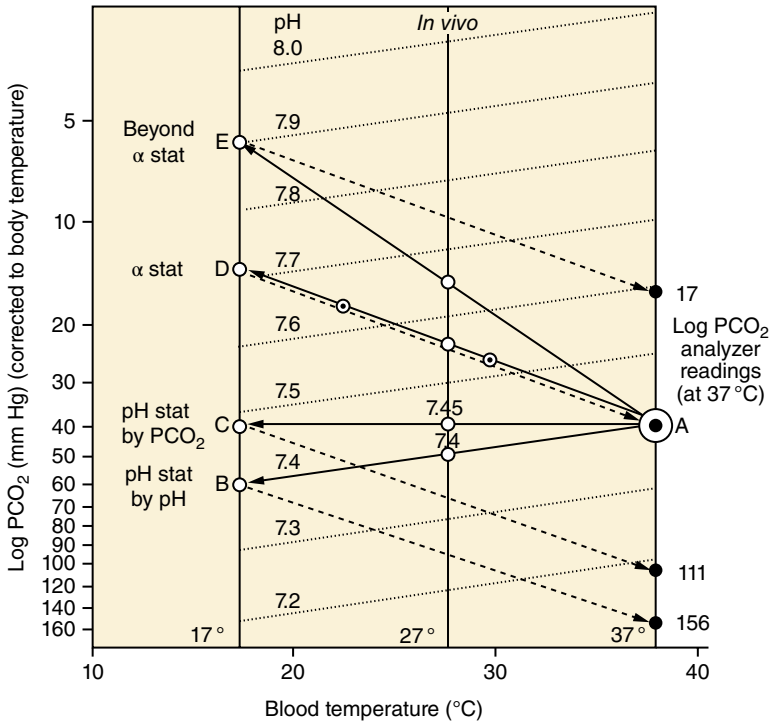


Figure 11.18 pH and PCO_2 change when blood temperature is varied between 17 and 37 °C. Point A is the starting point with pH 7.4 and PCO_2 of 40 at 37 °C. Points B, C, D, and E are the conditions the brain experiences at 17 °C with various blood gas management strategies. pH-stat management (correcting the pH and PCO_2 for temperature) results in an acid-base environment that is neutral, whereas α-stat management (not correcting for temperature) results in a very alkalotic environment at 17 °C. Warming the blood sample (as is done for blood gas measurement) results in very high PCO_2 values when pH-stat is used. The pH of blood becomes slightly more alkalotic with cooling owing to the decreased dissociation of hydrogen ions. (Source: Jonas [290]. Reproduced with permission of Taylor & Francis.)

In cyanotic infants with aortopulmonary collaterals, pH-stat management results in significantly improved brain oxygenation as measured by near-infrared cerebral oximetry [299]. A retrospective study of 16 patients revealed worse neurodevelopmental outcomes with alpha-stat management [257]. In a randomized prospective trial of pH vs. alpha-stat management in 182 infants <9 months of age, there was a strong trend toward improved outcomes with pH-stat management, including the earlier return of EEG activity, fewer seizures, and improved psychomotor development index [193]. Bellinger et al. [300], in their landmark study, examined the effects of alpha-stat and pH-stat on developmental and neurological outcomes after deep hypothermic CPB in infants. The Psychomotor Development Index scores of 110 patients did not differ significantly between the groups ($P = 0.97$). Bellinger et al. concluded that the use of alpha-stat or pH-stat strategy is not consistently associated with improved or impaired early neurodevelopmental outcomes in infants undergoing deep hypothermic CPB [300].

One reason for the differing results between pediatric and adult studies is that the increased cerebral blood flow produced by pH-stat management leads to a greater number of cerebral emboli in adults. Emboli occur much less frequently in children, and the primary etiology of neurological injury from CPB in pediatric patients is hypoxic-ischemic [301]. Thus, the increased cerebral blood flow observed on CPB with pH-stat management lessens this risk in children. Interestingly, this putative mechanism has been recently challenged by a study involving a controlled microembolic load and DHCA in pigs that revealed that pH-stat was still associated with improved outcomes when compared with alpha-stat [302]. Recent studies have also revealed a decrease in peak postoperative troponin levels, reduced ventilator dependence, and reduced ICU stays with pH-stat as compared with alpha-stat [303].

Currently, the preferred technique in adults is the alpha-stat method because it is believed that cell function and autoregulation are better preserved by maintaining neutral pH according to the temperature of the cell. In pediatric cardiac surgery, however, unlike adults, pH-stat enhances cerebral and systemic protection during DHCA. Most congenital heart surgery programs have reverted to pH-stat management. This necessitates careful attention to $PaCO_2$ during all phases of bypass, potentially reducing the sweep gas flow to decrease the efficiency of CO_2 removal, and often adding inspired CO_2 to the sweep gas of the bypass circuit, particularly in small infants.

Sickle cell disease

Sickle cell disease is an inherited hemoglobinopathy in which a mutation in the β-globin gene on chromosome 11 causes the sixth amino acid of the β-globin chain to be changed from valine to glutamic acid. The disease is inherited in an autosomal recessive pattern, with a homozygous form (Hgb SS) and a heterozygous form, or sickle cell trait (Hgb AS).

The sickle cell gene is most commonly observed in African populations, with 1 in 500 African Americans having Hgb SS, and 1 in 12 with sickle cell trait [304]. In the United States and most developed countries, there is now universal newborn screening for hemoglobinopathies, and sickle cell disease is, therefore, usually diagnosed at that time. After the normal postnatal decline in fetal hemoglobin (Hgb F) in the first 6 months, Hgb SS patients have Hgb S concentrations of 70–98%, and Hgb AS patients have Hgb S concentrations of 30–50%. Hgb S causes sickling of red cells, leading to chronic hemolytic anemia and impaired microvascular perfusion. This can result in end-organ dysfunction and permanent injury, including painful bony crises, splenic sequestration and autoinfarction, acute chest syndrome with hypoxemia, retinopathy, renal failure, pulmonary hypertension, and stroke. Hypoxemia, acidosis, cold temperature, hypovolemia, and microvascular stasis all promote sickling. Other less common forms of sickle cell disease are sickle cell-hemoglobin C disease (Hgb SC), and sickle cell-thalassemia variants. The reader is referred to excellent recent reviews for further detailed information about these disorders [304, 305]. Modern treatment for Hgb SS now includes chronic transfusion therapy to maintain the Hgb S at <30%, with Hgb levels of 9–10 g/dL. In addition, hydroxyurea is now commonly used in sickle cell disease because of its ability to increase the production of Hgb F, reduce Hgb S, and decrease the severity of disease manifestations. Hydroxyurea can substantially reduce the Hgb S percentage, and so this should be considered in the preoperative planning for these patients. The conditions commonly encountered for CPB – hypothermia, low flow, acidosis, and hypoxemia – all predispose to sickling, and a careful strategy is required to optimize outcomes in these patients [306, 307]. Although no universally accepted guidelines have been published, recent data and reviews provide important guidance. Careful consultation with the patient's hematologist and surgeon, and a clear strategy devised with the perfusionist, are essential when planning for CPB.

Exchange or straight transfusion has been used successfully for CPB surgery in homozygous sickle cell disease, either preoperatively, or in the operating room with the initiation of CPB [308, 309]. Preoperative exchange transfusion is cumbersome, expensive, and usually not necessary. If preoperative straight transfusion is utilized, the goals are to achieve an Hgb of 10 g/dL, with Hgb SS <30%. Other common approaches include a partial exchange transfusion performed at the time of initiation of CPB. CPB prime volume is increased to two to three times the patient's blood volume, with PRBCs and colloid or crystalloid calculated to achieve a Hct of 30% and Hgb S well below 30% on CPB. In addition, 25–33% of the patient's blood volume is diverted from the venous return upon initiation of CPB, and discarded instead of draining into the venous reservoir, further diluting Hgb S. Other recommendations for CPB are to perform the surgery at normothermia whenever possible and to limit hypothermia to mild (>32 °C) if it is needed. [307, 309]. If deeper levels of hypothermia are required, a more extensive exchange transfusion is necessary with Hgb S <10%. In addition, frequent arterial blood gases are measured on CPB with a goal of full arterial oxygen saturation (PaO_2 >100 mmHg), and mixed venous blood gases are also assessed with the goal of SvO_2 >75–80%. Maintaining full CPB flows at 2.4–3.2 L/min/m^2 or above, and perfusion pressures in the high normal range are also important. Finally, cardioplegia strategies may be altered, with some authors recommending only crystalloid cardioplegia, with an initial "warm" dose at 26–32 °C, to wash out any red cells from the coronary arteries before cold cardioplegia is given [307, 309]. As noted earlier, sickle cell trait (Hgb AS) patients may still have Hgb S concentrations of 30–50% at baseline, and, although asymptomatic under normal conditions, are at risk for sickling with CPB. Therefore, sickle trait patients should be approached in the same manner as homozygous sickle cell disease patients for CPB cases [309]. Using these CPB recommendations, Yousafi et al. reported outcomes for 21 pediatric and 26 adult patients with sickle cell disease or trait [309]. No patient had a perioperative sickling crisis; however, two patients had a stroke, and two had renal failure postoperatively. Chacon-Portillo and colleagues retrospectively reviewed 46 patients median age 1.3 years (range 3 days to 38 years) with sickle cell trait (80%), or sickle-beta thalassemia (20%-no homozygous Hgb SS patients) undergoing CPB surgery [310]. Exchange transfusion immediately before instituting CPB was accomplished in 65% of patients to achieve a targeted-on pump Hgb S of <30%. Four patients (9%) developed sickle cell complications, including two with acute chest syndrome, one with ischemic stroke, and one immune hemolysis. Three of four had exchange transfusion, and two of four had on bypass hematocrit slightly above 30%. Although numbers were small, the authors concluded that exchange transfusion did not alter the outcomes in this cohort. Regardless of the ultimate protocol for CPB management for the sickle cell patient, close vigilance in the postoperative period is critical, especially for acute chest syndrome with hypoxemia, the most common perioperative sickling complication [304]. Renal failure and stroke are also threats in the perioperative period after CPB surgery. Recommendations for sickle cell disease and CPB are summarized in Table 11.6. Published data about other hemoglobinopathies such as thalassemia are scant, and the anesthesiologist should consult with the patient's hematologist and surgeon when planning strategies for this rare situation [305]. The decision about whether to perform exchange transfusion should but subject to multidisciplinary discussion among the surgeon, anesthesiologist, hematologist, and perfusionist, and take into account the patient's baseline Hgb S%, and complexity of the planned operation, duration of bypass, and degree of hypothermia.

Cold agglutinins

Cold agglutinin disease in pediatric patients is most commonly observed after *Mycoplasma pneumoniae* infection, in as many as 55% of patients in the first 2 weeks of this disease [307]. Antibody levels peak in the third week and decrease significantly by 2–3 months after infection. Cold agglutinins are usually immunoglobulins of the IgM class and are characterized by reaction at cold temperatures with surface red blood cell antigens, causing activation of the complement pathway, with agglutination and hemolysis. Reported adverse effects during hypothermic CPB include massive hemagglutination, microvascular thrombosis and hemolysis, with coronary thrombosis, inability to deliver cardioplegia,

Table 11.6 Recommendations for homozygous (Hgb SS) or heterozygous (Hgb AS) sickle cell disease and cardiopulmonary bypass (CPB)

Preoperative	Intraoperative CPB	Postoperative
Maintain euvolemia with IV hydration Avoid hypoxemia, hypothermia, acidosis Consider straight transfusion to Hgb >10 g/dL and Hgb S <30% Exchange transfusion rarely indicated	Partial exchange transfusion with CPB: prime volume two to three times blood volume with PRBCs; target Hct on CPB >30%, Hgb S <30% Avoid hypothermic bypass, temperature >32 °C if needed Warm crystalloid cardioplegia for first dose Full flow CPB at all times >2.4 L/min/m^2 Avoid hypoxemia: PaO_2 >100 mmHg SvO_2 >75–80% Avoid hypotension Temperature corrected pH 7.35–7.45	Avoid hypoxemia; SpO_2 >95% at all times Maintain euvolemia Avoid hypothermia, maintain core temperature 36–37 °C Avoid acidosis: pH >7.35 Maintain Hgb >10 g/dL and Hgb S <30%

Hct, hematocrit; Hgb, hemoglobin; IV, intravenous; PRBCs, packed red blood cells; SpO_2, pulse oximeter saturation; SvO_2, mixed venous oxygen saturation.

and oxygenator failure. Typically, cold agglutinin disease is characterized by high antibody levels at 4 °C and low levels at normothermic temperature; however, the level of hypothermia at which agglutination occurs can vary, and when cold agglutinin disease is diagnosed preoperatively it is important to define the temperature range at risk. The true incidence of cold agglutinin disease in pediatric patients is not known, but it appears to be very low. Elective cases in the face of post-*Mycoplasma* cold agglutinin disease should be postponed. When the thermal threshold is defined, CPB temperatures are maintained well above that threshold. Patients with high titers and a warm temperature threshold are at the greatest risk, and consideration can be given to high-volume plasmapheresis preoperatively if surgery must proceed. Maintaining normothermia pre- and post-CPB is also important, as is a consideration for warm crystalloid cardioplegia. Occasionally cold agglutinins may only be suspected intraoperatively when agglutination occurs during hypothermic CPB. Rapid testing can be performed by most blood banks and clinical laboratories; increasing the temperature to the highest tolerable level should be done emergently in this situation. Recommendations for the management of cold agglutinins are summarized in Figure 11.19 [307].

Leukoreduction and irradiation of blood products

Leukoreduction of blood products (PRBCs, platelets, and whole blood) has been described in attempts to reduce the inflammatory response to CPB from leukocyte reduction, by employing leukocyte-reducing blood filters either before or during CPB. However, in the two controlled trials in pediatric patients, there were no clinical outcome differences in leukoreduced patients [311]. More commonly, leukoreduction is performed to provide "cytomegalovirus (CMV)-safe" blood products, as this virus is contained entirely in white blood cells [312]. Leukoreduction for all units of PRBCs, platelets, and whole blood has become standard practice in many hospitals because of the high prevalence (35–65%) of seropositivity for CMV in donated blood units. Despite this practice, 0.02–0.25% of blood units still test positive for CMV, and so transmission is still possible [312]. Patients who are or who may become transplant recipients may require CMV-negative blood confirmed by donor serology; local policies vary and need to be well understood by the anesthesiologist.

Irradiation of blood products (PRBCs, platelets, FFP, whole blood) prevents graft-versus-host disease from transfused leukocytes. This is a rare but serious complication and has resulted in uniform irradiation policies for high-risk groups, which include premature neonates and young infants in the first 3 months of life, immunosuppressed patients such as some transplant recipients, and those who have had blood donated by relatives [313, 314]. Irradiation causes several changes due to hemolysis of PRBCs, including potassium release, acidosis, increased lactate, increased free hemoglobin, and decreased glucose [315]. Hyperkalemia with K^+ levels over 20 mmol/L is common even with irradiated PRBC units less than 7 days after donation. Irradiated PRBC units should be checked for K^+ levels, and consideration should be given to washing the units before CPB, especially in neonates.

KEY POINTS: SPECIAL CPB MANAGEMENT ISSUES

- Warm or tepid temperatures are successfully used in pediatric cardiac surgery.
- DHCA remains a cornerstone of neuroprotection for complex cases involving aortic reconstructions, such as the Norwood procedures.
- Deep hypothermia involves complex management issues in respect of the maintenance of hematocrit, even cooling of the brain over 20 minutes using a pH-stat strategy, cold, normoxemic reperfusion, and the avoidance of hyperthermia postoperatively.
- RCP was developed in an attempt to provide continuous cerebral perfusion throughout the repair. A minimal flow of 40 mL/kg/min is required.
- To date, there is no proven superiority of one method over the other.

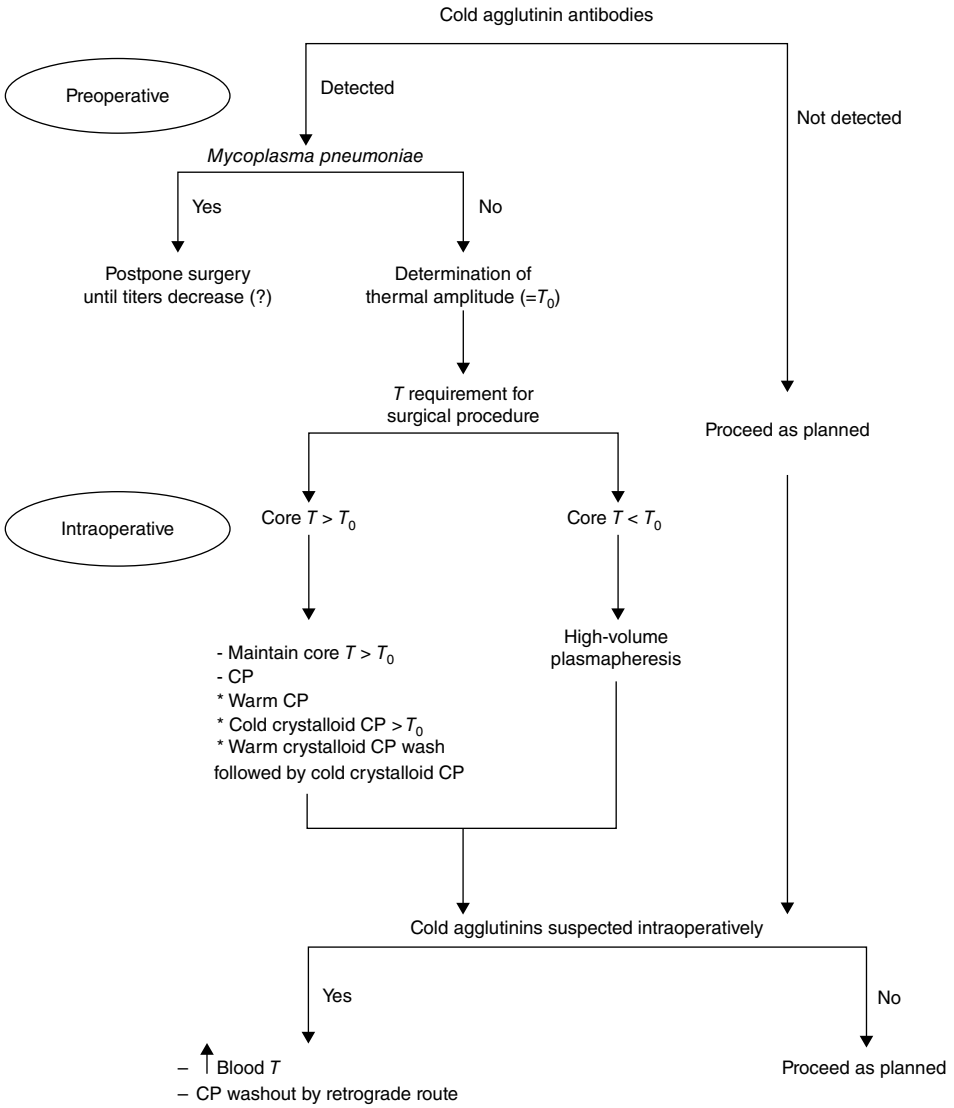


Figure 11.19 Perioperative management algorithm for cold agglutinin disease. T_0, cold agglutinin induction temperature; *T*, temperature on cardiopulmonary bypass (CPB); CP, cardioplegia. (Source: Daaboul et al. [307]. Reproduced with permission of SAGE Publications.)

Monitoring anticoagulation during and after CPB

Since the landmark 1959 paper by Keats and colleagues from Texas Children's Hospital, heparin reversal by protamine, and its assessment using the ACT has been the standard approach for confirming anticoagulation with heparin, and reversal of the heparin by protamine [63]. The celite ACT test with a target time of 400–480 seconds has remained the standard for initiation and maintenance of anticoagulation on CPB in many institutions for over 50 years. Reversal of the heparin effect is achieved with protamine, and return to baseline ACT serves as a confirmation of neutralization of this heparin effect. ACT is a point-of-care test performed by the perfusionist on a device often mounted on the CPB machine, and its rapid turnaround is unmatched by other tests. However, the ACT is only a gross measure of the initiation of clotting, will be affected by many factors other than heparin (e.g., thrombocytopenia or platelet dysfunction), and does not measure fibrinolysis or other aspects of clot persistence (clot strength). Several other point-of-care heparin and coagulation monitors will be discussed here; the reader is referred to Chapter 13 for additional details.

Point-of-care heparin–protamine titration systems for the measurement of plasma heparin concentrations (Hepcon, HMS Plus®; Medtronic, Inc., Minneapolis, MN, USA) perform an *in vitro* bedside assay to determine plasma heparin concentrations. Plasma heparin levels of 3.0 units/mL are considered adequate anticoagulation for CPB, and the use of this system is effective to titrate additional heparin doses during bypass. In a study of 44 patients under the age of 6 months undergoing CPB, Guzzetta et al. compared ACT, Hepcon, and direct plasma heparin concentration using an antifactor Xa chromogenic substrate assay [316]. ACT showed no correlation with plasma heparin concentration after the initial heparin bolus or during CPB; there was a

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modest correlation with one of the ACT methods just before termination of CPB. Hepcon demonstrated a good correlation with direct plasma heparin level measurement, as well as an acceptable bias by Bland–Altman analysis, with Factor Xa heparin levels higher by 0.49–0.67 units/mL than Hepcon heparin levels. Gautam et al. reported on 100 patients aged 1 month–5 years who had two different methods of protamine dosing compared, the first based on estimated blood volume of the patient plus CPB prime volume and the second based on patient blood volume alone [317]. Hepcon, ACT, and TEG (see later) were measured in both groups, and although protamine neutralization of heparin was successful by both methods, the authors concluded that the protamine dose calculated by Hepcon resulted in lower plasma protamine concentrations; excess protamine prolonged the clotting time (R value; see later) as measured by TEG. Therefore, heparin–protamine titration may result in more accurate maintenance of desired heparin levels during bypass, as well as avoiding excessive protamine dosing after neutralization.

Thromboelastography (TEG®; Medtronic, Inc.) and thromboelastometry (ROTEM®; TEM International GmbH, Munich, Germany) are related methods that measure clot initiation and maintenance of clot integrity and therefore provide a more complete profile of the coagulation system. TEG uses the shear elasticity of a 0.36 mL blood sample, measured by the constraint of rotation of a cup and pin as fibrin strands and then a platelet-fibrin clot forms, attached to a torsion wire transduced to an electronic signal that displays a plot [318] (Figure 11.20). Time to initiation of the clot, maximum clot strength, and breakdown as a result of fibrinolysis are measured. Heparinase can be added to the sample to eliminate the heparin effect, and kaolin to speed the initiation of clot formation to make TEG more of a real-time point-of-care test. Despite this, a minimum of 10–15 minutes are required to acquire data about the time of initiation, and the speed of initiation of clot, and 45–60 minutes to acquire a full profile that includes fibrinolysis. Data in the adult population demonstrates that TEG can guide the anesthesiologist as to what blood product (platelets, FFP, cryoprecipitate) and what dose to administer. TEG studies have demonstrated that the method is sensitive to reduced platelet number and fibrinogen concentration and that these parameters, especially maximum amplitude, correlated well with post-bypass bleeding [319]. Platelet count <120,000 L^{-1} and fibrinogen concentration of <100 mg/dL were predictive of bleeding and abnormal TEG results. More recent studies in high-risk pediatric cardiac patients have also demonstrated that a low maximum amplitude (MA) on the TEG is associated with an increased risk for bleeding [319, 320].

Thromboelastometry (ROTEM) is similar to TEG in that a small blood sample in a cup is rotated around a pin, but instead of a torsion wire, the formation of a clot (constraint of rotation of cup) is detected by an optical light-emitting diode detection system. This feature, and better fixation of the rotating pin, may make ROTEM more resistant to vibration and small movements, to make it more suitable for point-of-care testing in the operating room. The ROTEM tracing and parameters are similar to TEG (Figure 11.21) [321]. In addition to heparinase, cytochalasin D can be added to the test to discern fibrin polymerization early, with clot strength at 10 minutes having a strong correlation to clot strength at 30 minutes ($r = 0.91–0.97$, $P < 0.001$) [322]. This allows the test to be done during CPB with results that can be interpreted after about 15 minutes. The post-bypass ROTEM maximum clot firmness parameter correlated with bleeding in one small study [323]. A comparison of TEG and ROTEM parameters is given in Table 11.7 [324].

Because platelet defects, both in number and function due to activation from the bypass components and procedure, are the most common and serious cause of post-bypass

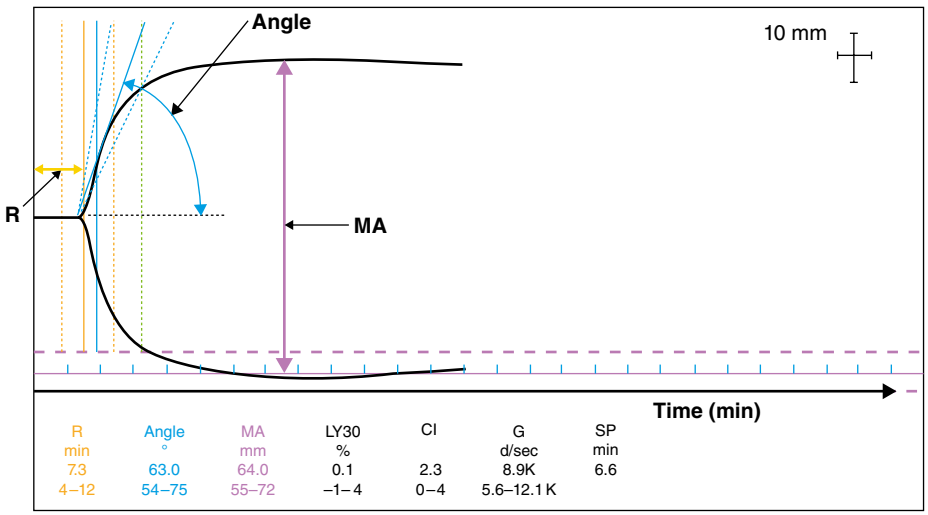


Figure 11.20 Normal thromboelastography tracing. R, reaction time (in minutes until first detectable levels of fibrin clot formation). Sensitive to heparin and coagulation factor levels. Angle – reflects fibrinogen activity, but it does not always correlate with direct measurements. MA, maximum amplitude – clot strength, the combination of platelet count and function plus fibrinogen activity. LY30, percent clot lysis after 30 minutes – measurement of fibrinolysis. G, clot firmness in dynes/second (d/sec): CI, coagulation index: complilation of R, K, angle, and A; SP (split point): time from sample placement (or activation with an exogenous procoagulant) until the earliest detectable resistance. (Source: Chen and Teruya [318]. Reproduced with permission of Elsevier.)

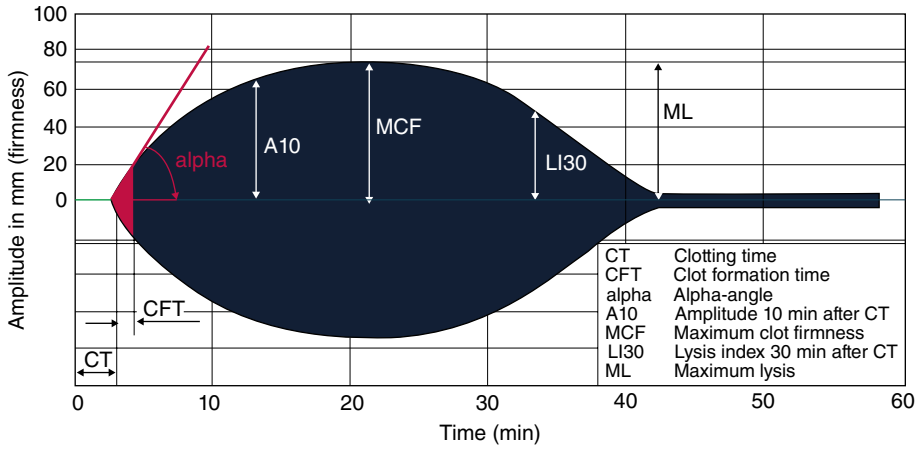


Figure 11.21 Normal ROTEM tracing. (Source: Rotem [321]. Reproduced with permission of Tem International GmbH.)

Table 11.7 Variables measured by the thromboelastography (TEG) and ROTEM

Variable	TEG	ROTEM
Measurement period	—	Reaction time (RT)
Time from start to when the waveform reaches 2 mm above baseline	R	Clotting time (CT)
Time from 2 mm above baseline to 20 mm above baseline	K	Clot formation time (CFT)
Alpha angle (°)	α (slope between R and K)	α (angle of tangent at 2 mm amplitude)
Maximum angle	—	CRF
Maximum strength	Maximal amplitude (MA)	Maximal clot firmness (MCF)
Time to maximum strength	—	MCF-t
Amplitude at a specific time	A30, A60	A5, A10
Clot elasticity	G	MCE
Maximum lysis	—	CLF
Clot lysis (CL) at a specific time (min)	CL30,CL60	LY30, LY45, LY60
Time to lysis	2 mm from MA	CLT (10% difference from MCF)

Source: A Practical Guide to Laboratory Hemostasis [324]. Reproduced with permission of Elsevier.
CLF, clot lysis fraction; CLT, clot lysis time; MCE, maximal clot elasticity.

coagulopathy in young infants [325], point-of-care platelet function tests have been proposed to guide the administration of platelets (Sonoclot®, Sienco, Inc., Boulder CO, USA; TEG PlateletMapping®, Medtronic, Inc.). Data are very limited in pediatric cardiac surgery, and to date these tests cannot be recommended as part of routine care [326, 327].

Each institution must develop an approach to monitoring coagulation for CPB cases to reduce unnecessary blood transfusion while achieving prompt hemostasis, and avoiding inappropriate protamine dosing, particularly for neonatal and other complex cases at high bleeding risk. The available evidence suggests that a heparin–protamine titration system to ensure accurate heparin dosing and reversal, combined with point-of-care clot formation and integrity tests such as TEG or ROTEM, may be best able to achieve this [328]. Irrespective of the testing regimen, recent data have confirmed the classical papers demonstrating that platelets are the primary defect, followed by hypofibrinogenemia, in complex cardiac surgery in infants [329]. See Chapter 16 for an extensive discussion of bleeding and hemostasis.

KEY POINTS: MONITORING ANTICOAGULATION DURING AND AFTER CPB

- For over 60 years the standard method has been heparin administration and protamine neutralization monitored by ACT.
- Heparin–protamine titration systems allow for more accurate heparin and protamine dosing.
- TEG and thromboelastometry allow more accurate blood product administration after bypass.

Complications and safety

The most frequent causes of death or injury related to CPB mishaps have been arterial embolism and consumptive coagulopathies. Other life-threatening events include thrombus in the extracorporeal circuit, inadequate pressures and flows, aortic dissections, separation of extracorporeal lines, drug administration errors, protamine administration during CPB, heparin overdose, transfusion reactions, negative pressure complications (principally air entrainment), electrical failure, and failure to provide gas exchange. The incidence of fatal accidents in recent surveys of adult and pediatric perfusion is in the range of 1 in 1,300 to 1 in 4,900 procedures. Serious or permanent injury is reported in 1 in 1,139 to 1 in 2,500 cases. Near misses or incidents occur in approximately 1 in 138 to 1 in 198 cases [330–332]. Pre-bypass checklists,

vigilance on the part of all members of the team, and the use of standard perfusion monitors and devices will minimize catastrophes.

The most common problems in pediatric practice are inadequate pressures or flow from either poor venous return (most often due to cannula placement) or problems at the arterial cannulation site (malposition of the aortic cannula, e.g., in the innominate artery with preferential perfusion of the right carotid; dissection or hematoma).

Most situations can be controlled by rapid recognition, correction, or – in rare cases – separation from bypass and restoration of normal circulation unless the aorta has been ruptured. A great deal of suspicion and good communication amongst the team are vital in this respect.

Emergency cardiopulmonary bypass

Patients at high risk for cardiopulmonary collapse during anesthesia induction or during surgical dissection should be prepared for emergent cannulation for cardiopulmonary bypass. Preoperative identification of these patients is critically important. Multidisciplinary planning among cardiac surgery, anesthesia, nursing and perfusion teams is important to resuscitate these patients. Other preoperative measures such as ultrasound or CT imaging of the femoral blood vessels to delineate their size and patency is important in case femoral cannulation is required. Cannulation strategy with appropriate femoral or other bypass cannulae available is essential. Early blood priming the bypass circuit before induction of anesthesia, presence of surgeon and perfusionist in the operating room, and having instruments and nursing and scrub personnel prepared are all essential preparations.

Conclusions and future perspectives

In summary, pediatric CPB is challenging as it extends the spectrum of extracorporeal circulation in many aspects. Familiarity with differences to adult bypass circuits and management is of the utmost importance and the team, consisting of cardiac surgeon, perfusionist, and anesthesiologist has to work very closely together to reach the goal of good perfusion practice. The results of this hard work are rewarding, however, and offer many children a better perspective and greater life expectancy. There are myriad variations in bypass technique, specific to each institution and often to each individual surgeon within an institution. No one technique has been conclusively proven to be superior to others with regard to myocardial and clinical outcomes; better neurological outcomes have been demonstrated with avoidance of extreme hemodilution and prolonged DHCA. Future directions lead towards a "goal-directed perfusion management" with special emphasis on organ protection and further technical advances in miniaturization of the CPB circuit size to reduce the use of blood transfusions and the inflammatory response. Together with the determination of a safe Hct limit, this may render the asanguineous neonatal CPB possible. A checklist approach is useful in developing the individual anesthesiologist's approach to CPB in children (see Table 11.6).

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

27 Newburger JW, Jonas RA, Soul J, et al. Randomized trial of hematocrit 25% versus 35% during hypothermic cardiopulmonary bypass in infant heart surgery. J Thorac Cardiovasc Surg 2008;135:347–54. Randomized trial demonstrating that higher hematocrit on bypass is associated with improved neurodevelopmental outcomes.

31 Andropoulos DB, Easley RB, Gottlieb EA, Brady K. Neurologic injury in neonates undergoing cardiac surgery. Clin Perinatol 2019;46:657–71. An updated review of potentially modifiable factors for neurologic injury in the perioperative period that the anesthesiologist can influence.

49 Manlhiot C, Gruenwald CE, Holtby HM, et al. Challenges with heparin-based anticoagulation during cardiopulmonary bypass in children: impact of low antithrombin activity. J Thorac Cardiovasc Surg 2016;151:444–50. A comprehensive study of antithrombin levels and their effect on heparin response and consumption. Neonates and young infant less than 6 months of age hage variable baseline antithrombin levels and heparin response.

94 Matte GS, del Nido PJ. History and use of del nido cardioplegia solution at boston children's hospital. J Extra Corpor Technol 2012;44:98–103. A comprehensive review of the rationale, composition, and technical aspects of preparing and delivering del Nido cardioplegia solution, which is increasingly used in congential heart surgery centers.

104 Nathan M, Levine JC, Van Rompay MI, et al. Impact of major residual lesions on outcomes after surgery for congenital heart disease. J Am Coll Cardiol 2021;77:2382–94. A major study of over 1,000 infants undergoing common repairs including tetralogy of Fallot, arterial switch operation, complete atrioventricular canal, VSD with arch reconstruction, and Norwood stage I palliation. Residual lesions diagnosed by echocardiography that were major or required reintervention were associated with significantly higher rate of adverse outcomes including days alive and out of hospital, and time on ventilator, ICU stay, and major complications including cardiac arrest ECMO cannulation, and neurologic morbidity.

109 Elliott MJ. Ultrafiltration and modified ultrafiltration in pediatric open heart operations. Ann Thorac Surg 1993;56:1518–22. Classic article describing techniques and uses of conventional and modified ultrafiltration.

132 Lorusso R, Raffa GM, Kowalewski M, et al. Structured review of post-cardiotomy extracorporeal membrane oxygenation: part 2-pediatric patients. J Heart Lung Transplant. 2019;38:1144–61. A comprehensive review of post-cardiotomy ECMO – indications, cannulation strategies, outcomes including survival to hospital discharge, and complications.

153 Faraoni D, Rahe C, Cybulski KA. Use of antifibrinolytics in pediatric cardiac surgery: where are we now? Paediatr Anaesth 2019;29:435–40. A contemporary review of antifibrinolytic strategy in pediatric cardiac surgery in the post-aprotinin era, with updated data on pharmacokinetics and dosing of epsilon-aminocaproic acid and tranexamic acid.

254 Wypij D, Newburger JW, Rappaport LA. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston circulatory arrest trial. J Thorac Cardiovasc Surg 2003;126:1397–403. The classic article demonstrating that prolonged circulatory arrest over about 41 minutes is associated with lower neurodevelopmental scores at age 4 years after the neonatal arterial switch operation.

273 Fraser C, Andropoulos DB. Principles of antegrade cerebral perfusion during arch reconstruction in newborns/infants. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2008;11:61–8. A presentation of the technical aspects of regional cerebral perfusion, and their effect on cerebral physiology as measured by cerebral oxygen saturation and transcranial Doppler cerebral blood flow velocity measurements.

CHAPTER 12

Multiorgan Effects of Congenital Cardiac Surgery

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Introduction

The diagnosis and surgical management of congenital cardiac disease in the pediatric patient present a profound challenge to a developmentally immature physiology. Associated congenital syndromes, chronic abnormalities in hemodynamics, and immature developmental physiology of the young child all result in the potential for multisystem aberration. The exposure of a patient in this relatively tenuous state to the systemic challenges associated with cardiopulmonary bypass (CPB) results in both short- and long-term challenges in the management of these children.

The systemic response to congenital cardiac surgery

CPB triggers complex cellular and humoral inflammatory responses designed to respond to noxious stimuli (Figure 12.1). Children are particularly prone to the effects of this response, due to the large relative surface area of bypass circuit, increased metabolic demand requiring higher flows, and developing organ systems particularly prone to injury [1]. These consequences of CPB predispose the pediatric patient to end-organ injury and multisystem organ failure (MSOF). The management of this end-organ dysfunction, which includes coagulopathy, pulmonary and myocardial dysfunction, renal insufficiency, and diffuse capillary leak, represents a major challenge in postoperative management.

Activation of complement, the kinin–kallikrein–bradykinin system, and the coagulation system results in a systemic response that is both highly redundant and multisystemic (Figure 12.2). These events are triggered immediately upon contact of the patient's blood with the foreign surfaces of the CPB circuit. Further activation occurs as a result of mechanical stress on blood components, hypotension, nonpulsatile perfusion, hypothermia, intestinal hypoperfusion, and systemic reperfusion following the release of the aortic cross-clamp. Additionally, the administration of heparin and protamine

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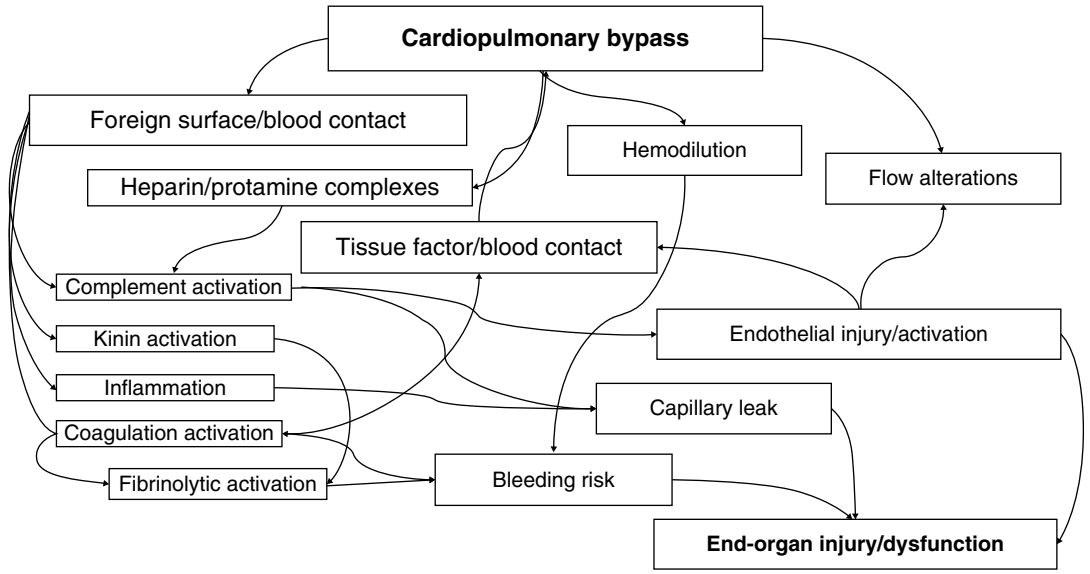


Figure 12.1 Summary of the multiple systemic pathways involved in the physiologic response to cardiopulmonary bypass (CPB). Activation of the contact system by elements of the CPB circuit produces an array of physiologic humoral activations. Dilution of coagulation elements by crystalloid solutions decreases coagulability of blood and contributes to bleeding risk. Alterations in flow, such as ischemia–reperfusion injury, and nonpulsatile flow produce changes in endothelial function, such as expression of tissue factor and disordered endothelial-dependent relaxation. Inflammatory cells, platelets, complement fragments, and cytokines mediate many of these pathways.

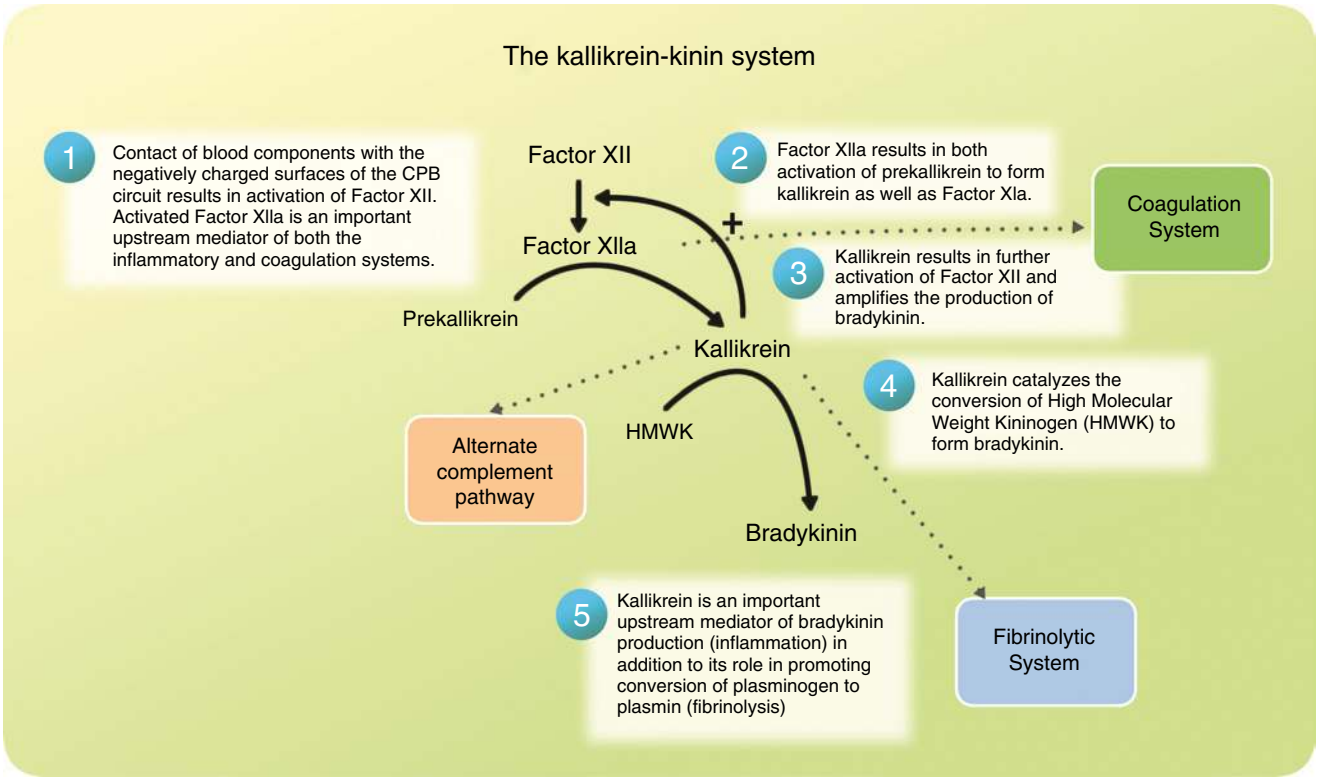


Figure 12.2 Diagram showing the initiation of the inflammatory cascades produced by contact of blood with nonbiologic elements of the CPB circuit. Note the central role of kallikrein.

during the course of cardiac surgery results in an increase in cellular and humoral processes that contributes to systemic inflammation and end-organ injury [1].

Systems mediating the systemic inflammatory response to CPB

Complement pathway activation

Exposure of blood to the components of the CPB circuit results in rapid activation of complement via the alternate pathway and initiates inflammation. While this component of the complement system is designed to respond to microbial cell-surface components and mediate the body's defense against microorganisms, it may also be activated by exposure of blood to foreign surfaces, endotoxin, and kallikrein [2]. This activation results in conversion of C5 and C3 to C5a and C3a, respectively. C3a and C5a are potent anaphylatoxins that activate and degranulate neutrophils and mast cells and initiate platelet aggregation. C5a and C3a also act directly on endothelium, producing increased vascular permeability and smooth muscle contraction. C5a primes monocytes and macrophages to greatly increase the production of tumor necrosis factor alpha (TNF-alpha) in the presence of endotoxin. This initial increase in TNF-alpha may represent an early central event in the upregulation of the systemic inflammatory response [3].

In addition to the activation of the alternate complement pathway by contact with foreign surfaces, the classical complement pathway further contributes to the systemic inflammatory response when activated by heparin–protamine complexes. Their presence results in generation of C4a and further increases in C3a production, resulting in increasing vascular permeability. These processes (C5a and C3a activation, TNF-alpha production) result in successive surges in humoral mediators of the inflammatory response: toxic oxygen metabolites, pro-inflammatory cytokines (interleukin-1 [IL-1], TNF-alpha, IL-6, IL-8, and lipopolysaccharide [LPS]), and anti-inflammatory cytokines, which limit systemic inflammation (IL-4, IL-10). The TNF-alpha levels increase dramatically following the initiation of CPB and peak at 2 hours and 18–24 hours postoperatively [4]. The levels of C5a and C3a are directly related to the duration of CPB, and infants exhibit a more dramatic increase than neonates [5]. Despite the known physiologic effects of these inflammatory mediators, attempts to correlate clinical outcomes with the degree of complement activation (using C3a and C5a plasma levels as markers) have led to inconsistent results [6, 7].

Activation of the kinin system

Kinins are polypeptides generated from kininogens following tissue injury or noxious stimulation. Their functions are incompletely understood, but are known to be involved in blood pressure regulation and mediation of inflammation through activation of G-protein–coupled B1 and B2 receptors. Kinins are potent vasodilators, which also increase vascular permeability, smooth muscle contraction, and neutrophil chemotaxis. While B2 receptors are constitutively expressed in most tissues, B1 receptors are induced and functionally expressed in the presence of inflammatory cytokines, endotoxin, and following tissue injury. The generation of kinins depends upon the contact of blood with the negatively charged surfaces of the CPB circuit and subsequent activation of factor XII (FXII) to FXIIa. FXIIa results in the production of kallikrein from prekallikrein, which then results in further activation of FXII and the production of bradykinin from high-molecular-weight kininogen (HMWK). This positive feedback loop amplifies the production of bradykinin, a potent mediator of both acute and chronic inflammation. Bradykinin, in turn, results in further generation of inflammatory cytokines and the endothelial release of nitric oxide and tissue-plasminogen activator.

Activation of inflammation

The response to CPB is also mediated by various cytokines, which facilitate communication between components of the immune and inflammatory systems. They are polypeptide hormones of low molecular weight (5–20 kDa) produced by macrophages, monocytes, lymphocytes, fibroblasts, and endothelium. They modulate humoral and cellular immunity in addition to the maturation and activation of immune cells. The plasma concentration of cytokines at baseline is in picomolar concentrations (10–12) and may increase up to 1,000-fold in the setting of injury or infection. Data regarding the degree of cytokine release following CPB and the ratio of pro-inflammatory versus anti-inflammatory cytokines are often conflicting owing to inconsistencies in the source, technique, and the timing of sampling. It is clear, however, that identifiable waves of cytokine release characterize the inflammatory response to CPB and that important clinical and laboratory consequences of this response are observable in the perioperative period. Additionally, the functions of individual cytokines are highly redundant and pleiotropic, which presents a significant challenge to those looking to mitigate their downstream effects for clinical benefit.

Endothelial injury

Normal endothelium is an important custodian of smooth muscle, producing vasoactive mediators such as nitric oxide and prostacyclin, which fine-tune microcirculatory function. Injury to this critical monolayer decreases the production of these vasodilatory mediators and increases the release of vasoconstrictors endothelin and thromboxane A2 [8]. Endothelin probably mediates increased pulmonary vascular resistance, as higher plasma levels are found in patients who develop pulmonary hypertension. In a swine model of renal injury following CPB, an endothelin-1 (ET-1) receptor antagonist reversed many changes associated with endothelial dysfunction and renal injury [9].

The pulmonary endothelium is responsible for breakdown of several potent vasoconstrictors: angiotensin, catecholamines, and eicosanoids. Its injury therefore results in sustained increases in pulmonary vascular resistance following CPB. Endothelial dysfunction results in increases in capillary permeability and interstitial edema in addition to microcirculatory dysfunction. Efforts to improve pulmonary flow during CPB [10, 11], or supplement the NO pathway with L-arginine [12, 13], may contribute to minimizing post-CPB pulmonary pathology.

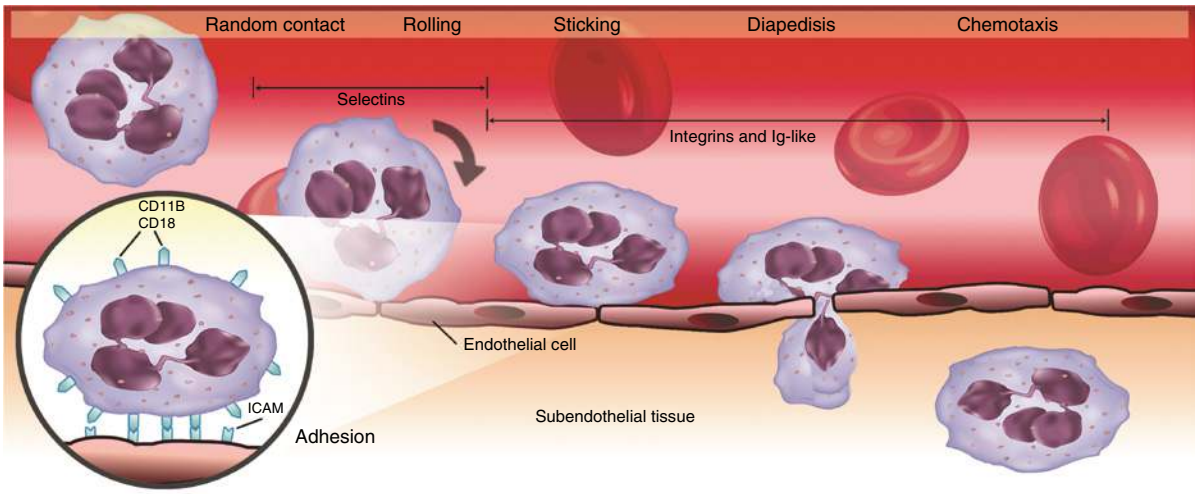


Figure 12.3 Neutrophil adhesion, diapedesis, transendothelial migration and chemotaxis. ICAM, intercellular adhesion molecule.

Neutrophil activation and sequestration

Neutrophil activation plays a pivotal role in ischemia–reperfusion injury and destruction of the extracellular endothelial cell matrix. CPB produces widespread activation of neutrophils and increased expression of adhesion molecules on neutrophils and endothelium. Activated neutrophils adhere to endothelium and migrate across interendothelial junctions to produce their effects in subendothelial tissues. Selectins, integrins, and immunoglobulins mediate neutrophil adhesion, migration, and chemotaxis (Figure 12.3). Notably, selectin expression increases substantially following CPB in pediatric patients and may be associated with clinical outcomes [14, 15]. Additionally, IL-1 and TNF-alpha result in increased ELAM-1 (endothelial leukocyte adhesion molecule-1) expression on endothelium, facilitating further the binding of neutrophils to the endothelium. Additionally, IL-8 promotes interaction of activated neutrophils with endothelial ICAM-1 receptors and results in further neutrophil migration to the extravascular space.

Endotoxemia

CPB decreases gastric mucosal pH and intestinal perfusion and increases intestinal permeability. Endothelial dysfunction decreases the release of nitric oxide and prostacyclin, thus increasing the vascular resistance in splanchnic beds. The resulting intestinal hypoperfusion allows translocation of predominantly Gram-negative bacteria. Endotoxin, the LPS component of the bacteria outer cell membrane, binds macrophages and monocytes and triggers further release of inflammatory mediators. Endotoxin is present in the circulation of 96% of children following CPB [16].

Endotoxin is a recognized prologue of inflammation in the setting of enteric pathology. Circulating endotoxin and inflammatory mediators (IL-1, IL-1beta, and IL-8) correlate with the severity of necrotizing enterocolitis (NEC) in newborns [17]. Children with greater endotoxin burden have higher serum levels of IL-6, more hemodynamic instability, and greater mortality [16]. Data suggest that milrinone may improve GI blood flow and thereby reduce endotoxemia and IL-6 levels in adults undergoing CPB [18]. Additionally, hypothermia during CPB has been associated with increased levels of endotoxin [19].

Activation of the coagulation system

Hemostasis is extensively altered during cardiac surgery. CPB produces widespread perturbations in platelet function, thrombin activation, endothelial function, and inflammatory cells.

Old and new models of coagulation

The familiar "coagulation cascade" (Figure 12.4) has served for years as an important educational paradigm in many respects. It has led to the development of our common coagulation tests, which have been useful in identifying deficiencies in the coagulation pathways. It has also been useful in identifying coagulation inhibitors. Yet, while abundantly referenced formally and discussed informally, the traditional cascade model does not explain some essential observations. For example, patients with FXII or prekallikrein deficiency typically do not have bleeding problems, a conclusion unlikely to be drawn by tracing the pathways of the cascade. Likewise, patients with FVIII or FIX deficiencies (hemophilias A and B) have severe coagulopathies, also unexplained directly by the cascade. The cascade model does not account for the roles of cells and tissues where the coagulation reactions occur.

Consequently, pedagogy in coagulation has shifted toward the *cell-based model of coagulation*, originally proposed by Hoffman and Monroe in 2001 [20] (Figure 12.5A and B). It is useful to carefully step through the cell-based model, because doing so will explain the abovementioned limitations in the traditional cascade model. In this revised model, coagulation proceeds by the processes of *initiation, amplification, and propagation* [20–22]. In the *initiation* phase, elements of the intrinsic pathway (FXII, FXI, prekallikrein, HMWK), which are important for the generation of kinins as mentioned above and for initiating coagulation in a laboratory glass vessel, are not essential for the initiation of coagulation *in vivo*. Rather, the *initiation phase* begins when FVIIa contacts tissue factor (TF) at the site of vascular

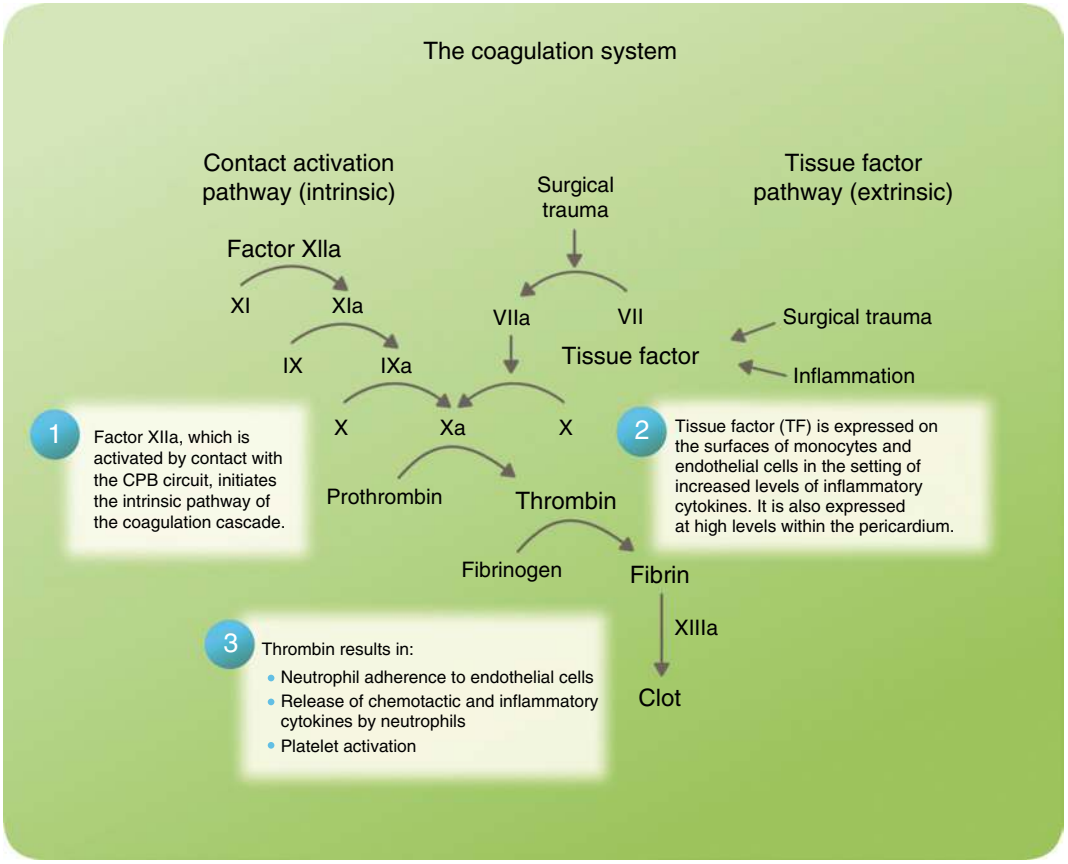


Figure 12.4 The familiar coagulation cascade model showing intrinsic and extrinsic pathways. Rectangles denote enzymes or their corresponding zymogens, and ovals represent cofactors. As mentioned in the text, this model has provided much utility in the past, but fails to account for some simple clinical observations. Examples include failure to fully explain why contact factor deficiencies are not associated with significant bleeding and why factor VIII and IX deficiencies are associated with severe bleeding.

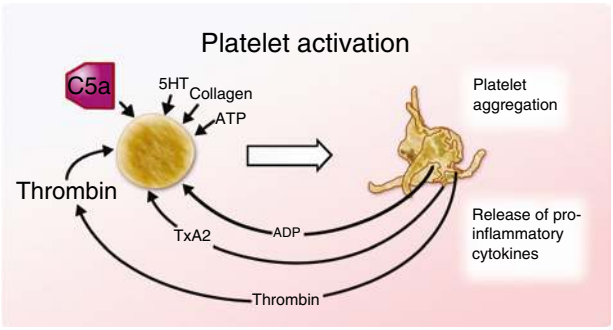
injury. The resulting TF–FVIIa complex activates FX and FIX. The resulting FXa is sufficient to generate a small amount of thrombin (FIIa), localized to the site of injury, since FIIa diffusing away from the site is significantly dampened by antithrombin (AT), and the FVIIa–TF–FX complex is rapidly inhibited by tissue factor pathway inhibitor (TFPI).

In the *amplification phase*, the thrombin that is present activates FV and FVIII, important cofactors for FXa and FIXa, which form complexes on platelet surfaces to increase further generation of thrombin. Platelet activation results in a proliferative increase in phospholipid surface rich in phosphatidylserine, essential for these enzymatic complexes to bind and function, and produces secretion of additional coagulation factors (FV, FVIII, von Willebrand factor [vWF]) from platelet granules [23]. Thrombin also provides an important positive feedback loop by activating FXI, which also generates additional FIXa.

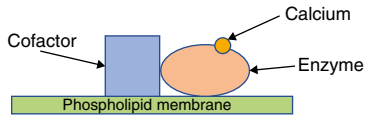
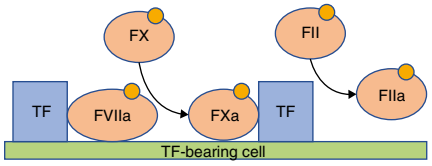
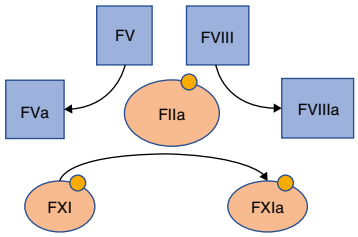
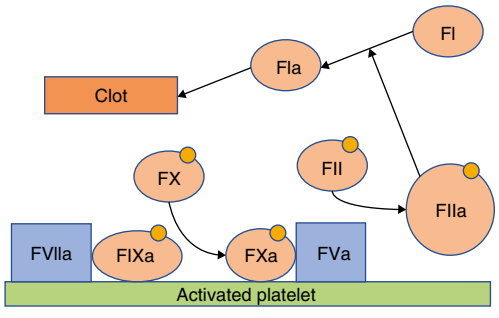
Once these elements are in place (activated platelets, activated cofactors FVa and FVIIIa, thrombin, and FXa and FIXa), the *propagation phase* is marked by sustained thrombin generation provided by the prothrombinase complex (FXa–FVa). The success of this phase depends mostly on activity of the tenase complex (FVIIIa–FIXa), which generates continued amounts of FXa. The endpoint of coagulation is this local, sustained generation of thrombin, which catalyzes conversion of fibrinogen into fibrin monomer, spontaneously polymerizing into fibrin strands to form a stable clot. Thrombin also activates FXIII, which cross-links and stabilizes fibrin clot, increases neutrophil adherence to endothelium, and stimulates neutrophil release of chemotactic and inflammatory cytokines.

Coagulation is normally confined to the region of injury by several mechanisms. Inactivated platelets do not express significant levels of phosphatidylserine on the plasma surface of their membranes and, therefore, do not support coagulation factor activity very well. Upon activation, the platelet outer membrane expresses phosphatidylserine and serves as a platform for the formation of coagulation complexes. Normal endothelium does not express TF, nor does it contain appreciable amounts of exposed phosphatidylserine and, therefore, does not support coagulation. Therefore, any FVIIIa–FIXa or FVa–FXa that diffuse away from the site of injury will not generate thrombin. AT and heparin cofactor II rapidly attenuate any stray FIIa. Thrombin also forms a complex with thrombomodulin on endothelial surfaces, activating protein C, an important control element that cleaves FVa and FVIIIa into inactive fragments.

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(A)

Process	Description	Diagram
General scheme	Assembly of enzyme with cofactor, on phospholipid surface, with calcium ions	
Initiation	FVIIa/TF complex generates Fxa, which generates a small amount of thrombin at the site of injury	
Amplification	Activation of FV, FVIII, and FXI by thrombin (FIIa); activation of platelets with secretion of multiple factors	
Propagation	Sustained generation of FXa on activated platelet surface by FVIIIa/FIXa complex allows for continued production of the prothrombinase complex (FXa/FVa), which produces massive sustained thrombin generation. Thrombin in such quantities converts fibrinogen to fibrin, which polymerizes to form a clot.	

(B)

Figure 12.5 (A) Widespread platelet activation is triggered in the setting of cardiopulmonary bypass (CPB) by the activity of c5a, thrombin, and the secretion of platelet activating factor (PAF) by endothelium. Platelet activation results in a dramatic change in platelet morphology, exocytosis of dense granules and alpha granules, and aggregation. Aggregation is mediated by von Willebrand factor (vWF) and glycoprotein IIb/IIIa receptors that bind fibrinogen. The phospholipid surface of the platelet is the site of assembly of enzyme complexes essential to clot formation. (B) The revised model of coagulation, the cell-based model. Essential to understanding this pathway is the assembly of enzyme complexes on phospholipid surfaces with the requirement for calcium ions. The pathway consists of three overlapping phases: initiation, amplification, and propagation. In the *initiation* phase, exposure of blood to tissue factor (TF) produces a small amount of activated factor X (FXa). This, with FV results in the formation of a small amount of local thrombin (FIIa). In the *amplification* phase, this amount of thrombin is insufficient to produce significant fibrin clot, but it activates FV and FVIII, greatly increasing their activity, and activates FXI, which provides a positive feedback loop by activating FIX. Platelets are activated by contact with the site of injury and provide a massively greater phospholipid surface for the assembly of the complexes in the *propagation* phase. Here, sustained thrombin generation is maintained by continued generation of the FVIIIa/FIXa complex and the prothrombinase complex (FVa/FXa).

CPB and the coagulation system

CPB produces profound alterations in coagulation factor levels and activities, which are quantitatively different in children when compared to adults [24–27]. Because of the large relative pump-prime volume, hemodilution is a much greater cause of decreased factor levels after CPB in children [27]. Dilution and consumption of coagulation factors is the major cause of post-CPB coagulopathy in children [28].

Despite high levels of heparin during CPB, thrombin is generated [25, 29]. It is tempting to assign thrombin generation during CPB to activation of the contact pathway, since blood is exposed to the nonbiologic surfaces of the CPB system. However, patients with contact factor deficiencies (FXII, prekallikrein, FXI) still manifest thrombin generation during CPB [30, 31], indicating that the contact pathway is not driving coagulation during CPB. Rather, exposure of blood to TF is likely the cause. Inflammatory cytokines produce TF expression on endothelium and monocytes, and contact of blood with the nonendothelialized tissues in the mediastinal cavity and elsewhere produces thrombin activation [32]. Thrombin then perpetuates both inflammatory and thrombotic processes. This prothrombotic state may persist for several hours postoperatively, even in the setting of clinical bleeding. In infants, TF expression may extend into the postoperative period [32].

Platelets are activated during CPB and extrude their contents [1, 24]. Glycoprotein receptors become expressed on the platelet surface. Released factors include platelet factor-4, beta-thromboglobulin, and vWF from alpha granules, while the platelet surface expresses adhesion molecules such as P-selectin. Platelet activation and adhesion to endothelium results in additional expression of transmembrane receptors that mediate binding and transmigration of activated neutrophils. This results in additional recruitment of neutrophils to the extravascular space. Furthermore, platelets of young infants are generally less reactive than those of older children and adults, and decreased platelet activation, as measured by changes in adhesive receptor density, has been observed following CPB in infants [33].

Recent attention has been paid to acquired von Willebrand disease (aVWD), represented by loss of high-molecular-weight vWF multimers, in children with congenital heart defects. Reportedly, aVWD is common in this population, both before and after surgery [34–36], but interestingly did not seem to correlate with clinical evidence of bleeding, possibly since endothelial secretion of vWF occurs during surgery due to the stress response [35–37], thus attenuating the effect of a preexisting aVWD. The frequency of aVWD among pediatric patients on other means of extracorporeal circulation, such as *extracorporeal membrane oxygenation* (ECMO) or ventricular assist device (VAD), has been reported at 100% [38], potentially implicating the role of shear stress on blood components as a possible contributor to loss of the high-molecular-weight multimers of vWF. See Chapters 11 and 16 for further discussion of bleeding and coagulation.

Mitigating the deleterious effects of CPB

Practitioners have sought to develop effective means of mitigating the systemic response following CPB in children. Practices include perioperative corticosteroids, modified ultrafiltration (MUF), protease inhibitors, and biocoating of CPB circuitry. Although many such strategies achieve reduction in the levels of various inflammatory markers, studies demonstrating improvement in relevant clinical outcomes show more modest results. Two methods commonly in use include perioperative glucocorticoids and MUF. It is clear that effective modulation of the systemic inflammatory response to CPB in clinically meaningful ways remains elusive.

Corticosteroids

Perioperative corticosteroids are often intended to reduce the systemic inflammatory response and its deleterious effects. Corticosteroids act through nuclear transcription factors, whose binding to promoter regions decreases expression of pro-inflammatory mediators. While studies have demonstrated reductions in inflammatory mediator expression, there is little consensus on the clinical benefits of steroid administration in this setting. Furthermore, there is tremendous heterogeneity among the patient management regimens, and sample sizes are often small. These issues complicate the efforts of systemic reviews and limit their utility.

Thus, a comprehensive review of steroids to minimize the impact of CPB is beyond the scope of any one chapter. With this in mind, however, it is possible to summarize some common themes in our current understanding. In 2012, Pasquali et al. conducted an analysis of data from the Pediatric Health Information Systems (PHIS) and Society of Thoracic Surgeons Congenital Heart Surgery (STS-CHS) Databases [39]. They reported results from 30 pediatric cardiac centers across the United States from 2004 to 2008, comparing outcomes of neonates receiving methylprednisolone on the day prior to or on the day of surgery. The study population included 3,180 neonates from 25 centers. They found no difference in mortality or length of hospital or intensive care unit (ICU) stay between the methylprednisolone and control groups. More recently, Bronicki and colleagues [40] published their findings from a meta-analysis of randomized prospective trials involving steroid treatment to mitigate the impact of inflammation in pediatric CPB. Their findings showed a significant heterogeneity between trials, necessitating the use of a random-effect model. Nonetheless, the authors observe a significant improvement on short-term fluid balance associated with steroid treatment, but no measurable impact on infection or mortality. Likewise, a recent Cochrane review [41] reported findings from a meta-analysis of current pediatric steroid trials, showing that steroid therapy may decrease the duration of mechanical ventilation, but did not show a measurable impact on mortality. Such recent data regarding the lack of clinical effectiveness of perioperative steroids is leading many centers to reconsider their routine use.

Modified ultrafiltration

Hypothermia, hemodilution, and the profound inflammatory response to CPB result in widespread capillary leak and increase in total body water. Dilution of plasma proteins, particularly in the smallest patients, results in further increase in interstitial fluid. Management of total body fluid overload

can be especially challenging in the postoperative period due to concomitant myocardial dysfunction and renal immaturity often seen in the pediatric patient. MUF removes water, low-molecular-weight solutes, and inflammatory mediators via filtration immediately following CPB. It also allows return of the contents of the CPB circuit to the patient in a concentrated form [42]. MUF has been shown in an animal model to attenuate pulmonary-derived inflammatory markers (based on reductions in IL-6 and IL-8 concentrations obtained by bronchoalveolar lavage) seen following bypass. In this model, MUF reduced pulmonary vascular resistance [43]. MUF has been shown to be effective in reducing weight gain during CPB, decreasing levels of activated complement C3a and C5a, and reducing concentrations of pro-inflammatory cytokines [44]. While some studies have shown little appreciable difference in the levels of inflammatory mediators following MUF, others have shown increase in plasma concentrations of IL-6, IL-8, and neutrophil elastase [45].

Clinically, MUF reduces total body water, decreases transfusion requirement, reduces postoperative coagulopathy, and decreases inflammatory marker levels after CPB [46]. A 2011 survey of international pediatric perfusion practice found that 71% of centers reported using some form of MUF [47]. While the clinical outcome differences associated with MUF are not dramatic, the beneficial effects of MUF may be more easily demonstrated in neonatal patients requiring a longer duration of CPB [48].

Protease inhibitors

Protease inhibitors are a class of drugs whose primary role is inhibition of various signaling pathways. Aprotinin, originally marketed as a kallikrein and plasmin inhibitor, decreases transfusion requirements following CPB, but also has substantial anti-inflammatory effects [49, 50]. Two randomized trials have shown decreased hospital stay and cost associated with aprotinin [51, 52]. Another blinded, controlled, randomized, prospective trial in 60 children weighing under 10 kg reported decreased ventilator time [53]. Both aprotinin and tranexamic acid (not a protease inhibitor) reduce expression of pro-inflammatory genes and increase expression of anti-inflammatory proteins [54].

Since 2006, aprotinin use has severely declined, and aprotinin is now unavailable in many countries, including the United States. The departure of aprotinin has been driven mostly by epidemiologic evidence for renal failure in adults [55–58]. Whether the same risk transfers to the pediatric population is unclear: Three retrospective studies did not identify aprotinin as an independent risk factor for perioperative renal failure in children [59–61]. However, another retrospective pediatric study reported an association between aprotinin and perioperative renal failure when compared with aminocaproic acid, after controlling for confounding variables [62].

Biocompatible CPB circuits

Efforts to improve CPB circuit biocompatibility are often anticipated to decrease activation of cellular and humoral inflammation and attenuate end-organ injury associated with CPB. Although the initial rationale for heparin coating of CPB circuitry was related to the anti-thrombotic effects of heparin, the use of heparin-coated CPB circuit components has reduced complement activation, cytokine production, and improved pulmonary function [63–65]. Heparin-coated circuits also appear to adsorb lipoproteins, which may create a circuit surface that approximates that of cell membranes [66]. A recent small randomized study of perfusion circuits coated with a novel ternary polymer (SEC-1) showed significantly decreased inflammatory markers and improved preservation of multiple coagulation elements [67].

Though definitive data on clinical outcomes in children regarding heparin-bonded circuits are lacking, adult data suggest that biocompatible circuits are associated with reduction in RBC transfusion, re-sternotomy, duration of mechanical ventilation and ICU length of stay, and inflammatory response following CPB [68, 69]. The clinical impact of biocompatible perfusion circuitry in children warrants further study, particularly in high-risk patients.

KEY POINTS: THE SYSTEMIC INFLAMMATORY RESPONSE AND CONGENITAL CARDIAC SURGERY

- Cardiac surgery and bypass induce complex cellular and humoral inflammatory responses.
- Inflammatory events are initiated by contact of blood with foreign surfaces, heparin–protamine complexes, endotoxin, and transfusion.
- Endothelial damage induces diffuse capillary leakage and coagulation system activation.
- Platelet activation results in coagulation system activation and recruitment of additional inflammatory cells.
- Activated neutrophils cause proteolytic tissue injury, capillary leak, and increased pulmonary vasoconstrictor response.
- Cardiac beta-adrenergic receptors decrease in number and efficiency during bypass.
- Evidence for use of glucocorticoids is equivocal.
- MUF removes free water and inflammatory mediators after CPB.
- Heparin-bonded circuits improve laboratory markers of inflammation, with modest or equivocal improvements in clinical outcomes.

Clinical effects of congenital heart surgery on hemostasis and thrombosis

These major physiologic disturbances of the inflammatory and coagulation pathways produce significant morbidity in the form of hemorrhagic and thrombotic complications. Perioperative risk of bleeding and thrombosis increases in both severity and frequency with decreasing age of the child [26, 70–73]. Infants under 1 year of age experience average blood losses within the first 24 hours after surgery of about 40 cc/kg, which is about half of the patient's blood volume [73]. Perioperative thrombosis is also associated with significant morbidity, sometimes severe [74–78]. Venous thrombosis in children is a potentially devastating complication of congenital heart surgery and is reported to occur in as many as

16% of cases [79–81]. Central venous thrombosis and massive thrombotic disease in multiple organs occur with highest frequency in the youngest children and can yield catastrophic sequelae [33, 82, 83].

Unique aspects of pediatric coagulation

It is important to understand that, like many other organ systems, the hemostatic system of young infants differs significantly from that of older children and adults [21, 84, 85], giving rise to a concept known as "developmental hemostasis" (Figure 12.6). Healthy infants exhibit levels of the contact factors (FXII and FXI, HMWK, prekallikrein) that are 40–50% of adult levels at birth, and approach adult levels by 6 months of age. This profile is also followed by the vitamin K-dependent factors (FII, FVII, FIX, and FX) [84, 86–88]. FV, FVIII, and vWF reach adult levels more rapidly, and, as is the case for vWF, can exceed adult levels. Coagulation inhibitors (AT-III, C1 inhibitor, heparin cofactor II, protein C, and protein S) again follow the pattern of the contact and vitamin K-dependent factors [84]. Fibrinogen and plasminogen, although present at nearly adult levels in the term newborn, exist in forms that differ in their post-translational modification [89, 90]. Accordingly, laboratory reference ranges need to be based on age-matched samples from normal children.

Hemostasis in congenital heart disease

Congenital heart disease (CHD) imposes additional modifications on pediatric hemostasis (Table 12.1). In cyanotic children, polycythemia further dilutes coagulation factors. Decreased levels of FV, FVII, and FVIII and increased fibrinolysis, thrombocytopenia, and abnormal platelet function are frequently present and correlate with the degree of cyanosis [91]. Thrombocytopenia resulting from decreased platelet survival and fibrinogen dysfunction complicate the hemostatic picture and contribute to increased risk for bleeding [92, 93]. Children with CHD have increased incidence of heritable coagulopathies [94, 95] and combined deficiencies or partial deficiencies of FVIII, FXI, and FXII [96]. As mentioned above, loss of high-molecular-weight vWF multimers, representing a form of aVWD, is often observed in children with cardiac defects [97].

Table 12.1 Effects of cyanosis on coagulation physiology

Thrombocytopenia
Decreased platelet survival
Acquired von Willebrand disease
Fibrinogen dysfunction
Low-grade consumptive coagulopathy
Decreased coagulation factor levels
Accelerated fibrinolysis

Hemostatic anomalies of cyanosis are widespread and complex, and involve multiple elements of the coagulation and fibrinolytic systems [92, 93].

Risk factors for hemorrhagic complications in pediatric cardiac surgery

Numerous studies have identified clinical risk factors for hemostatic complications after pediatric cardiac surgery. In their classic study of over 500 pediatric patients, Williams et al. found that postoperative bleeding is associated with higher hematocrit, complex surgery, lower platelet count, and duration of circulatory arrest, but younger age was the most significant contributor [98]. Since then, other multivariate analyses have revealed that hypothermia, surgical complexity, high preoperative hematocrit, low platelet count, and decreased platelet function were highly correlated with

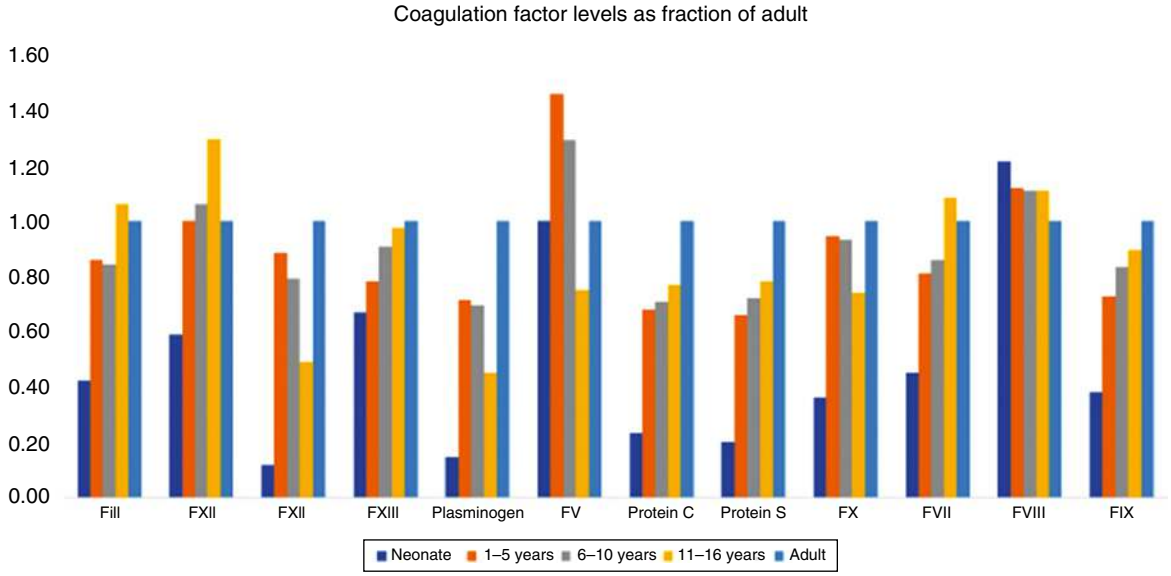


Figure 12.6 Developmental hemostasis. Factor levels in infants and younger children are generally lower than those of adults and evolve with age. Laboratory factor measurements and assays of coagulation need to be standardized for appropriate age groups. (Source: Data from Attard et al. [84].)

AL Grawany

Box 12.1: Coagulation system and cardiac surgery

- Coagulation system of infants and children is unique
  - Lower levels of many factors
  - Expression of differently processed forms of some factors
- Congenital heart disease imposes changes on coagulation system:
  - Frequent concurrent deficiencies of many factors
  - Cyanosis-induced decreases in factors V, VII, and VIII
  - Increased fibrinolysis
  - Low-grade disseminated intravascular coagulation (DIC)
  - Decreased platelet number and function
- Cardiac surgery imposes changes on the coagulation system of children:
  - Hemodilution
  - Fibrinolysis
  - Platelet dysfunction
  - Thrombin generation and factor consumption

blood loss and transfusion [70, 73, 98–101]. Some evidence suggests postoperative bleeding risk may vary among different ethnic groups [102]. Box 12.1 summarizes coagulation system changes in pediatric cardiac surgery.

Transfusion, inflammation, and outcomes

Transfusion alone appears to exacerbate the systemic inflammation of cardiac surgery. Transfusion following cardiac surgery is associated with various markers of inflammation [103], and with clinical outcomes such as longer ventilator times [104–106]. Univariate analyses show that red cell transfusion is associated with nearly every complication of congenital heart surgery, and transfusion is strongly associated with infectious complications, after controlling for confounding variables in a propensity analysis [107]. The authors have argued transfusion-related immunologic responses alone are good reasons to optimize transfusion management [105, 106, 108].

Transfusion in pediatric cardiac surgery

The rational approach to a bleeding pediatric cardiac surgery patient represents a significant clinical challenge for which the literature often provides limited prospective data. In a study with 75 children, platelet transfusion was most effective for post-CPB bleeding in patients under 8 kg. Continued bleeding was improved with cryoprecipitate but was made worse by plasma in this study [70]. Plasma is often ineffective in children probably because higher doses are required than the usual 10–15 mL/kg [109, 110]. Plasma added to the bypass prime may be beneficial, but the effect seems confined to the smallest patients [111, 112]. Fibrinogen concentrate has been proposed as an alternative for cryoprecipitate, but efficacy appears to be best for the adult cardiac surgery population [113–117], as data in children do not currently support its use [118].

While transfusion is frequently required in children in order to maintain adequate oxygen delivery, efforts should be made to reduce the volume of transfusion required. In a recent systematic review [119] of 299 studies of transfusion optimization from 22 countries, the authors concluded that the following efforts have merit in managing perioperative bleeding: antifibrinolytic drugs, objective transfusion guidelines, point-of-care testing, MUF, and circuit optimization. A large amount of heterogeneity regarding end point definition, patient population, and management schema and frequently small trial sizes made definitive conclusions difficult.

Still unclear is the issue of liberal versus restrictive transfusion thresholds. Although the literature on transfusion thresholds in adults is rapidly expanding, similar studies in children with CHD are fewer and less conclusive. Cholette [120] provides a recent summary of the pediatric cardiac surgery literature on restrictive versus liberal transfusion thresholds, summarizing the four existing studies [121–124] at the time. Despite concerns regarding exclusion criteria and small study size, the authors concluded that a more restrictive transfusion regimen (target hemoglobin 7 g/dL for biventricular repairs, 9 g/dL for cavopulmonary surgeries) may be well tolerated or even advantageous in these populations. They issue caution, however, that these results need to be validated and reproduced in larger trials and by other investigators before practice guidelines can be issued.

Objective, laboratory-guided transfusion algorithms have shown significant benefit in adult cardiac surgery [125], but it is difficult to extrapolate these conclusions to children, since adult and pediatric cardiac surgery are qualitatively different [126, 127]. Furthermore, not all reports of transfusion algorithms in children have shown positive results [128]. To be clinically useful, laboratory-guided protocols must rely on some reproducible, widely accessible metric. Routine coagulation tests, thromboelastography (TEG), and platelet count can predict postoperative bleeding in children after CPB [129, 130], which assists clinicians somewhat in identifying patients at risk. The use of TEG to specifically guide transfusion practice in pediatric cardiac surgery has been reported, with generally favorable results [28, 117, 131, 132]. A 2-year retrospective study of an objective transfusion algorithm in pediatric cardiac surgery has shown a significant savings of red cells, cryoprecipitate, and plasma and a 75% reduction in mortality following implementation of the algorithm [133]. In a recent review, the authors summarize a very broad literature, which includes the use of factor concentrates, but continue to emphasize the recurring observations that algorithms need to be institution-specific and that a transfusion-guided algorithm is superior to non-algorithm-guided transfusion [134].

Antifibrinolytics in pediatric cardiac surgery

Thrombin generation during CPB, and kinin activity from kallikrein activation, produce plasmin and thus activation of the fibrinolytic pathway. Accordingly, antifibrinolytic drugs (aprotinin, aminocaproic acid, and tranexamic acid) have long been useful adjuvants for limiting blood loss due to cardiac surgery. In general terms, their efficacy in children has been less consistent than in adults. Unlike adults, most children do not exhibit profound fibrinolytic activity after CPB [33, 72], and consequently, efforts to reduce bleeding by the

use of antifibrinolytic drugs are usually less effective in children than in adults [52, 135–139]. Some evidence in children suggests that fibrinolysis alone does not correlate with blood loss or transfusion in children [72]. The literature on antifibrinolytics for pediatric cardiac surgery is very broad, with much heterogeneity in end point definition and treatment protocols; therefore, the interested reader is referred to an excellent recent review [140].

When it was still available, aprotinin has been used in pediatric cardiac surgery, despite lack of the Food and Drug Administration (FDA) approval for pediatric use. Endpoints of blood losses and transfusion appear not as striking as those for adults, and a wide range of dosing schemes has been reported. Many prospective pediatric trials report hemostatic benefits with aprotinin [141–143], but most show equivocal results [52, 135–138, 144–146]. One of these studies [146] was terminated early by the FDA due to growing safety concerns in adults [55–58]. Nevertheless, beneficial effects of aprotinin in children extend beyond hemostasis. As mentioned previously, decreased hospital stay, shorter ventilator time, and decreased cost have been associated with aprotinin in children [51–53]. These improvements are likely a result of the anti-inflammatory effects of aprotinin, producing improved organ preservation and suppressed response to extracorporeal circulation.

The lysine analogs (aminocaproic acid and tranexamic acid) have been the only antifibrinolytics in clinical use since 2006. The lysine analogs probably do have efficacy in children, but less than that of aprotinin [147–149]. As with aprotinin, the efficacy of lysine analogs in children has been inconsistently reported, and differs between subgroups. Pediatric use of aminocaproic acid has been reported, but many of these studies were performed in the 1960s and 1970s, when surgical, anesthetic, and perfusion techniques were quite different than they are today [150, 151]. Williams et al. compared aminocaproic acid versus placebo control in a nonrandomized study involving 140 children and demonstrated nonsignificant decreases in blood losses and transfusion requirements [152]. Tranexamic acid has shown efficacy in children undergoing redo cardiac procedures [139], both in cyanotic and noncyanotic patients [153]. An earlier study of pediatric use of tranexamic acid was only able to demonstrate a reduction in postoperative blood loss in a subset of cyanotic children [154]. In a nonblinded trial, both aminocaproic acid and tranexamic acid were found to be equally beneficial in 150 cyanotic children [155]. The overall conclusion regarding the currently available antifibrinolytics (lysine analogs) is that these agents are safe and effective in the pediatric population [140].

MUF in pediatric cardiac surgery

As mentioned previously, MUF concentrates hemostatic factors and removes inflammatory mediators, thus reducing postoperative coagulopathy [156]. MUF appears to be most effective at improving hemostasis for the smallest infants [48, 157, 158]. Bando et al. compared MUF after CPB against conventional ultrafiltration and observed a 2.5-fold decreased risk of red cell transfusion and 6-fold decreased risk of coagulation factor transfusion with MUF [48]. Other investigators have shown similar improvements in post-CPB coagulopathy or transfusion requirements with MUF [159–163]. Additional benefits include improved hemodynamics and cardiac performance [159, 160, 163–165], decreased ventilatory support [48, 163], and shortened hospital stay [44, 162, 163] (Table 12.2). These effects have not been reported in all studies [157, 166]. A meta-analysis of eight MUF studies showed improved hematocrit and hemodynamics compared with standard ultrafiltration, but later end points were equivocal [167].

Table 12.2 Reported benefits of modified ultrafiltration

Concentration of red cells and coagulation factors
Decreased red cell and coagulation factors
Decreased need for inotropic support
Shorter ventilator times
Shorter ICU stay
Shorter hospital stay

Modified ultrafiltration after CPB improves not only hemostasis and transfusion, but has benefit in other organ systems, possibly due to decreased levels of inflammatory mediators, decreased capillary leak, and improved myocardial performance [156].

Other methods to minimize transfusion

Investigators have reported successful use of alterations in perfusion techniques, some of which avoid transfusion altogether, even in very small infants. Minimizing the volume of the pump prime [168–171], or use of a miniaturized bypass circuit [171, 172], has shown efficacy for reducing transfusion in small children. Alterations in pump composition such as a remote pump head resulted in no transfusion for 122 of 178 infants under 5 kg [173]. Use of washed red cells [174], fresh whole blood [71, 170, 175], heparin-coated circuits [176], use of an autologous blood prime [177], and anticoagulation management based on heparin concentration rather than ACT [178] have all reported efficacy in the pediatric population. However, practice guidelines have yet to be issued for most of these techniques often due to small study size, heterogeneity of end point definition and patient management protocol, possibility of publication bias, and lack of reproducibility of the results.

Other hemostatic agents

Recombinant activated factor VII (rFVIIa) has been used with increasing frequency as a rescue hemostatic agent in cardiac surgery for about the past two decades. Case reports of its use in pediatric cardiac surgery abound [179–183]. Serious concern exists regarding perioperative thrombosis, but the anecdotal nature of case reports and small case series makes it difficult to evaluate thrombotic risk associated with this agent, since it is typically administered to patients in dire need, who are likely to be at increased risk for thrombosis. To deal with this issue of confounding, a recent propensity analysis of 143 subjects receiving rFVIIa matched 1 : 2 with controls was reported by Downey and colleagues [184], who observed significant morbidity associated with the use of rFVIIa, including an independent risk for thrombosis. The rational use of rFVIIa in pediatric cardiac surgery has been

reviewed [185, 186]; the authors emphasize the need for randomized trials to clarify efficacy, subgroup analysis of population at risk, and the realistic assessment of thrombotic complications. Furthermore, a Task Force has been formed by the Congenital Cardiac Anesthesia Society, assigned to monitor the literature and issue recommendations as data become available [186].

Low antithrombin-3 (AT3) levels may place very young children at increased risk for bleeding, since such deficiency decreases the efficacy of heparin and therefore results in greater coagulation activation during CPB, with corresponding increase in coagulation factor consumption. Recent investigations have identified low AT3 as an independent risk factor for transfusion following cardiac surgery [29, 187], and a prospective trial of recombinant AT3 has reported efficacy specifically for small infants when this deficiency can be identified preoperatively [188]. Supplemental AT3 has also shown efficacy in the setting of ECMO [189].

Desmopressin has minimal hemostatic effects in adult cardiac surgery, and its specific impact in the pediatric population is probably also modest at best [190–193]. The use of other factor concentrates (fibrinogen concentrate, prothrombin complex concentrate) in pediatric cardiac surgery has been recently reviewed [118, 194]. These agents, initially proposed as rescue treatments for refractory hemorrhage, are now appearing in transfusion algorithms as standard treatments. The authors emphasize the need for high-quality studies of safety and efficacy, with standardized definitions of outcomes, prior to issuing any evidence-based recommendations.

Thrombosis in pediatric cardiac surgery

Thrombosis is frustratingly common in children with CHD since it is associated with significant morbidity [74–78]. In a series of single ventricle patients, systemic-to-pulmonary shunt occlusion accounted for 9% mortality during a 6-year follow-up [195]. Other authors report a 14% post-discharge mortality in a similar series, 81% of which was sudden and unexpected. Aspirin did not alter risk in this population [196]. In long-term studies, thrombosis has been identified as the first [197] or second [198] most common cause of late mortality in Fontan patients. Echocardiographic evidence of thrombus exists in as many as a third of asymptomatic children following the Fontan operation [74], with venous thromboembolism and stroke occurring in 19% of these patients [78]. The vascular access necessary for catheterization procedures is associated with a high rate of thrombosis [78], and post-thrombotic syndrome frequently complicates the clinical course [199]. Furthermore, reported incidence rates of thrombosis vary widely between institutions [74, 200–203], complicating comparisons between studies and interpretations of their results.

Risk factors for thrombosis in children with CHD

Thrombosis has some identifiable risk factors. Petaja et al. describe thrombotic events heralded by hypofibrinolysis in a small series of 10 neonates undergoing cardiac operations [33]. In this study, central venous thrombosis was associated with increased PAI-1, AT3, and protein C levels. In another case series of children with thrombosis and CHD, both acquired and inherited risk factors were found to be significant [200]. Some of these factors included multiple cardiac catheterization procedures, presence of a central venous line, pulmonary stenosis, aortic coarctation, and systemic infection. However, this study identified only 59 subjects with thrombosis and CHD, and an analysis of the interaction between environmental and genetic variables was not performed. Steen and colleagues recently confirmed the strong contribution of a central venous line to thrombosis risk in their cohort of 851 critically ill children [204]. Other risk factors identified in their cohort included longer ventilator times and ICU stay, low cardiac output syndrome, sepsis, catheter-associated blood stream infection, and cardiac catheterization. Interestingly, CPB was observed to have a protective role in thrombosis in this population.

Ali and colleagues recently reported thrombosis outcomes from their cohort of 369 pediatric subjects, 18% of whom experienced thrombosis [205]. Thrombosis in their population was associated with cyanosis, neonatal surgery, preoperative antiplatelet or anticoagulant therapy, and post-CPB transfusion. Transfusion was also identified as a thrombotic risk factor in a previous study of 138 children [206]. In other reports, markers of inflammation such as elevated free heme [207] or C-reactive protein levels [75] may also predict risk. Recent evidence is emerging that red cells probably contribute to coagulation activity [208], and some studies report that red cell transfusion increases thrombosis risk in pediatric surgery [208–212].

The role of genetic thrombophilias, such as FV Leiden (FVL), as a risk factor in this population has been evaluated, but the findings are difficult to interpret [81, 83]. Petaja's group reported central venous thrombosis in 20 of 1,591 pediatric patients undergoing CPB [83]. Of these, 12 were tested for activated protein C resistance, and 2 were positive. Ong et al. [81] screened a group of 200 consecutive pediatric cardiac surgery patients for FVL, but found the mutation not to be significantly associated with thrombotic risk. Protein C sensitivity, the laboratory coagulation phenotype which is reduced in the presence of the FVL mutation, has been associated with the degree of cyanosis in children with CHD, independent of FVIII levels and the presence of FVL [213], suggesting that cyanotic children are at decreased risk for thrombosis. Box 12.2 summarizes risk factors for thrombosis.

Box 12.2: Risk factors for thrombosis in children with congenital heart disease

- Presence of a central venous line
- Multiple intravascular interventions
- Pulmonary or aortic stenotic lesions
- Cyanosis
- Polycythemia
- Cavopulmonary anastomosis

KEY POINTS: EFFECTS OF CONGENITAL HEART SURGERY ON COAGULATION, HEMOSTASIS, AND THROMBOSIS

- Coagulation in cyanotic CHD is altered by cyanosis and surgery overlaid upon normal developmental coagulation.
- Bypass induces activation of the coagulation and fibrinolytic systems, placing cyanotic, thrombocytopenic infants at the greatest risk for postoperative hemorrhage.
- Lysine analogs have efficacy in bypass, especially cyanotic or resternotomy patients.
- Aprotinin improves hemostasis and hemodynamics and reduces inflammatory response and ICU stay.
- MUF improves hemostasis and other clinical outcomes.
- Thrombosis is a source of significant morbidity, and it is incompletely understood.
- Although treatment guidelines have been issued, primary prevention of thrombosis in children with CHD suffers from lack of strong supporting data.

Pulmonary effects of congenital heart surgery

Neonatal and pediatric pulmonary physiology: a compromised state

All physiologic systems carry an inherent amount of reserve, which is the capacity to increase their function to maintain homeostasis in the setting of a physiologic compromise. The pulmonary system is indeed able to compensate for injury by increasing ventilation and redistributing pulmonary flow. However, there are numerous features of the pediatric pulmonary system that place infants and children at increased risk of pulmonary failure in the setting of systemic injury (Table 12.3).

Metabolic compromise: The demands placed on the respiratory system of children are greater at baseline than those of adults, because of the increased metabolic rate of childhood [214]. Infants and young children, being in the active phases of growth and development, consume two to three times as much oxygen on a per kilogram basis, and generate correspondingly more carbon dioxide than do older children or adults [215]. Furthermore, hypoxic and hypercapnic drive of ventilation is attenuated in infants compared with older children or adults [216, 217]. Compromise of ventilation will therefore lead to respiratory failure sooner, and failure will accelerate faster in children, especially infants.

Table 12.3 Respiratory physiology in neonates and small infants

- Increased physiologic demands due to growth and development
- Mechanical compromise of chest bellows
- Metabolic compromise of diaphragm
- Decreased total lung capacity and functional residual capacity (FRC)
- Closure of smaller airways at FRC
- Atelectasis from surfactant deficiency
- Shunting due to retained lung fluid
- Decreased 2,3-diphosphoglycerate shift of fetal hemoglobin
- Pulmonary vascular disease from lesions with pulmonary overcirculation

Mechanical compromise: Air movement in and out of the lungs is driven by muscular actions on the bony structures of the chest. The diaphragm is the principal muscle of ventilation, but intercostals, scalenes, sternocleidomastoid, and even pectorals can be recruited in sequence as respiratory function demands. In children, the horizontal positioning of the ribs, and the increased compliance of nonossified bone, renders the intercostals and other accessory muscles at a distinct mechanical disadvantage [218]. Hence, the diaphragm must assume a greater share of respiratory work, and recruitment of accessory muscles offers less of an advantage.

The diaphragm of the infant, however, is less able to sustain increased aerobic work than that of the older child. Small children are also less able to increase their tidal volumes and therefore must increase minute ventilation by increasing in respiratory rate. The diaphragm and intercostal muscles of young infants have fewer of the type I, slow-twitch fibers than do the corresponding muscles of older children or adults [219]. These fibers are uniquely capable of higher oxidative capacity and offer a degree of insurance against fatigue when ventilatory demands are increased.

Ventilatory compromise: The resting ventilation of infants and young children differs markedly from that of older children in its classic spirometry. Because total lung capacity (TLC) is an effort-driven parameter, the TLC of an adult on a weight basis is much greater than that of a small child. Functional residual capacity (FRC) is defined as the lung capacity at which the elastic recoil forces of the lung and the passive recoil of the chest wall are equal and represents the volume in the lungs at the time of end expiration during quiet breathing. For infants and small children, FRC is significantly reduced; hence, a hypoventilating or apneic infant sequesters a disproportionally smaller reserve of intrapulmonary oxygen than an older child, leading to a more rapid development of hypoxemia [220, 221].

The closing volume of an infant's smaller airways is within the range of the infant's normal tidal volume [217, 220]. This means that during normal ventilation, some of the smaller airways close, resulting in air trapping. A specific lung volume is therefore not in communication with extrapulmonary air, possibly leading to atelectasis, ventilation–perfusion mismatching, and hypoxemia. Awake infants can re-establish their lung volumes by crying, deep vital capacity breathing, sighing, and movement, all of which are diminished or ablated by iatrogenic interventions such as anesthesia and sedation.

While small airway resistance contributes about 20% to the total airway resistance of the adult airway, these smaller airways contribute about half of the total airway resistance in infants [222–224]. Therefore, inflammatory injury to the lung, which results in small airway edema and lumen narrowing, makes a greater contribution to obstructive airway disease in smaller children. In the cardiac setting, this is highly relevant,

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as the inflammation associated with CPB and edema resulting from volume overload or increased pulmonary venous pressures are common.

The lungs of children have not finished growing. Although the major parts of the bronchial tree are formed during gestation, expansion of the alveolar population continues into the eighth year of life. Pulmonary vessel growth follows the development of alveoli. Smooth muscle development in pulmonary arteries of normal lungs is complete in adolescence.

Compromise of neonatal oxygen delivery: Very young infants can experience transpulmonary shunting, hypoxemia, and impaired oxygen delivery for other reasons. A newborn infant's lungs occasionally retain residual lung fluid, which contributes to transient tachypnea of the newborn [225]. This is often, but not always, self-limiting. Atelectasis in the first few days of life in term neonates or in preterm infants due to surfactant deficiency can also contribute to shunting [226]. Fetal hemoglobin has a significantly attenuated shift of its oxygen affinity in the presence of increased 2,3-diphosphoglycerate, which can compromise neonatal oxygen delivery in the setting of anemia or tissue hypoxia states [227].

Compromise arising from CHD: CHD further imposes another set of unique compromises to the pediatric pulmonary system. Pulmonary hypertension, most often arising from preexisting pulmonary vascular disease (PVD), is a frequent and often predictable sequela of pulmonary overcirculation, and portends significant perioperative morbidity [228–230]. PVD develops as increased pulmonary flow produces a recognized histologic pattern of pulmonary vascular remodeling. PVD increases in severity with both the duration and magnitude of excessive pulmonary blood flow.

In normal neonates, pulmonary vascular endothelium and vascular smooth muscle continue to develop into their mature phenotypes after birth and throughout the first years of childhood. When pulmonary flow is excessive, a different developmental trajectory is followed, with histologic evidence of medial hypertrophy, intimal hyperplasia, and decreased numbers of interacinar arteries being evident within months [231]. A histologic grading system, known as the Heath–Edwards classification, is used to assign a severity score to these changes (on a scale of 1–6). The Heath–Edwards grade predicts reversibility of PVD changes upon correction of excessive pulmonary flow. Pulmonary resistance is increased in PVD, and pulmonary vessels in PVD have increased sensitivity to vasoconstrictive stimuli of hypoxemia, hypercarbia, and acidosis, placing the patient with PVD at significant risk for perioperative cardiac failure [232]. Indeed, pulmonary hypertension, regardless of cause, continues to be a major risk factor for heart failure and other cardiac complications in patients with CHD. However, as hemodynamic data from the catheterization laboratory correlates with histologic grade, and lung biopsy carries significant risk, biopsy is not routinely used to assess prognosis in univentricular heart surgery [231, 233–236].

Cardiac performance significantly impacts pulmonary function. Increased pulmonary venous pressure, whether from arrhythmia, valve dysfunction, systolic dysfunction, or obstructive lesions, results in increased lung water and interstitial edema [237]. In the cardiac surgical setting, this can have disastrous effects on pulmonary compliance and gas exchange, elevating the work of breathing for what is often an already compromised patient. This is discussed in greater detail below. Cardiac surgeries which result in alterations of thoracic venous or lymphatic drainage (i.e. cavopulmonary connection or thoracic duct injury) may result in pleural effusion and/or chylothorax, which is exacerbated by the endothelial dysfunction associated with CPB. Postoperative prolonged pleural effusions are a significant source of prolonged mechanical ventilation and hospital stay [238–240].

Pediatric cardiac surgical patients often have impaired nutritional status, an often under-appreciated aspect of clinical care [241]. Approximately one in four children with CHD meets the criteria for failure to thrive within the first year of life, and half of those with single ventricle physiology require supplemental tube feeding [242]. The consequences of delayed growth and suboptimal nutrition for the cardiorespiratory system are not simply a matter of size [243]. Respiratory muscle drive and cardiac performance are measurably impaired in malnutrition [70, 244–246]. Both humoral and cell-mediated immune suppression render the malnourished child susceptible to perioperative infection [246–248]. Growth failure in the congenital heart surgery population has been associated with longer hospital length of stay, increased risk for infection, worse neurodevelopmental outcome, and mortality [242].

Children with congenital heart malformations often have other associated anomalies of the head, neck, mandible, teeth, and upper airway, both congenital and acquired. CHARGE, VACTERL, and Trisomy 21 frequently have associated malformations, which can make it difficult to secure the airway by the standard means of direct laryngoscopy [249–253]. With many children with CHD undergoing numerous cardiac surgeries, acquired respiratory tract disorders are increasingly common. Recent retrospective studies have shown a rate of acquired airway abnormality of 6.7%. The most common acquired airway abnormalities were vocal cord paralysis, bronchomalacia, and subglottic stenosis. All of these disorders can complicate airway management with many children having a combination of acquired and congenital airway abnormalities [254]. When these difficulties are appreciated, alternative approaches of airway management can be considered. If such difficulties are not appreciated, these associated anomalies may lead to prolonged apnea and failure to oxygenate or ventilate. When extubation is planned in the operating room, a greater degree of ventilatory performance is probably prudent to prevent the urgent need for reintubation under hurried circumstances.

It is therefore no surprise that children with CHD face a perioperative course fraught with potential pulmonary complications. Indeed, pulmonary complications represent significant sources of perioperative morbidity and mortality, increasing in severity and frequency with the decreasing age of the child [255–258]. In a study of nearly 700 children with CHD, preoperative respiratory insufficiency predicted the longest postoperative length of ICU stay [259].

Effects of CPB on pulmonary physiology in children

CPB and pulmonary vascular resistance

The obligatory mechanical support of the circulation during repair of congenital heart lesions is by no means a benign intervention. The coagulation system is severely attenuated while the entire blood volume of the patient is circulated in an elaborate system of plastic polymers and uncoated steel for an unspecified duration, during which time the entire patient is intentionally cooled to nonphysiologic temperatures. During much of this time, there is often no coronary flow, pulmonary flow is almost completely arrested, and perfusion to the remaining vital organs loses the pulsatile waveform under which these organs have thrived and evolved. Blood in contact with TF-bearing surfaces is often returned directly to circulation, and hemolysis is generated from suctioning and blood–air contact. Reperfusion and rewarming release the heralded cascade of ischemia–reperfusion responses, and post-bypass transfusion brings a flood of transplanted cells and proteins from a genetically distinct host. The lungs, now receiving 100% of the cardiac output (in a two-ventricle repair), bearing a massive area for gas exchange in a delicate capillary bed, and having an exquisitely sensitive arterial tree, respond profoundly to these perturbations, both local and remote.

Increased PVR, therefore, frequently complicates the postoperative care of pediatric cardiac surgery patients and represents a major risk factor for morbidity [260–262]. In various pediatric cardiac populations, increased PVR is associated with prolonged duration of ICU stay, prolonged duration of mechanical ventilation, and increased postoperative mortality [259, 260, 263–266]. It is a gross simplification to attribute the important postoperative increase in PVR to a single vasoactive mediator or process. Direct causes of increased PVR in the postoperative patient are quite numerous and include increased reactivity of the pulmonary vasculature, duration of CPB, hypothermia, acidosis, endothelial dysfunction, and preexisting PVD [260].

The endothelium is a pivotal tissue in the pathophysiology of elevated PVR following cardiac surgery. Through its secretion of vasorelaxant prostanoids and nitric oxide, the endothelium guards against unopposed vasoconstriction mediated by catecholamines, angiotensin, and endothelin [267]. This relaxant function is acutely disrupted by CPB [10, 268–270]. Although the cellular and subcellular mechanisms responsible for CPB-induced endothelial dysfunction have not been completely characterized, pulmonary ischemia–reperfusion injury is thought to be crucial in its etiology, despite early conjectures that the bronchial circulation provided adequate maintenance of pulmonary perfusion during CPB [10, 271]. Continuous perfusion of the lungs during CPB has been shown to improve oxygenation and decrease duration of postoperative mechanical ventilation in children [11, 272]. In fact, the perfusate need not even be blood; in a small prospective trial, lung perfusion with blood-free organ preservation solution during CPB resulted in improved oxygenation and decreased inflammatory response [272]. Laboratory studies have provided evidence for calpain and NF-κB as molecular mediators responsible for this ischemia-related increase in PVR [273, 274] (Table 12.4).

Table 12.4 Effects of cardiac surgery on lung physiology in children

- Ischemia–reperfusion injury
  - Impaired endothelial-dependent relaxation
  - Increased vasoreactivity of pulmonary vasculature
  - Increased lung water
- Impaired gas exchange
- Reduced lung compliance
- Decreased surfactant production and quality
  - Atelectasis of lung segments or lobes
  - Transpulmonary shunting
- Loss of lung volumes from deflation during cardiopulmonary bypass or presence of devices

Management of post-CPB pulmonary hypertension

Because CPB-induced increase in PVR is the result of a complex interplay of inflammation, reperfusion, and endothelial dysfunction, clinicians have successfully intervened with therapies directed toward a multitude of cellular and physiologic pathways. General measures include optimization of hematocrit, pH, ionized calcium and other electrolytes, temperature, adequate ventilation, high-dose narcotic, neuromuscular blockade, and treatment of arrhythmias. Pulmonary vasodilators (nitric oxide and its donors, phosphodiesterase inhibitors (PDEIs), and prostaglandin analogs) and inotropic support constitute the mainstay of specific therapy, as discussed below [275]. Additional adjunctive treatments involving anti-inflammatory agents [276], antioxidants, and protease inhibitors have shown some usefulness. In practice, pulmonary hypertension and right ventricular failure often involve multimodal management with a variety of agents and therapies [274, 277, 278].

Soon after the discovery of nitric oxide as the fundamental endothelial-derived vasodilator, inhaled nitric oxide (iNO) was employed as an agent to treat pulmonary hypertension [279, 280]. Nitric oxide is a small molecule that diffuses rapidly across membranes and has a biological half-life of only a few seconds owing to its rapid binding and inactivation by hemoglobin. It binds reversibly to and activates soluble guanylate cyclase, which catalyzes the conversion of guanosine 5′-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). This subsequent messenger activates cGMP-dependent protein kinase, which phosphorylates various proteins and causes vasodilation in multiple vascular beds [281]. Because the duration of action of nitric oxide is so short, inhaled NO (iNO) has the advantage of selectively dilating pulmonary arteries.

Clinical use of iNO has expanded dramatically since its discovery, because of its relatively low toxicity at doses less than 20 ppm, selectivity of the pulmonary vascular bed, efficacy in numerous settings, and ease of administration in ventilated patients [282–284]. In pediatric cardiac surgery, iNO has shown efficacy in reducing pulmonary pressures and improving oxygenation and right ventricular function [285–287]. Patients most likely to respond to iNO appear to be those with elevated preoperative PVR, although some with the highest PVR may be unresponsive [288, 289]. However, despite the efficacy of iNO in improving pulmonary resistance and hemodynamics in the acute postoperative setting, there are limited data from prospective, randomized

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trials [290]. A Cochrane review was inconclusive, owing to heterogeneity of populations, inherent publication bias, and lack of quality data [291]. Because the cost of administration of iNO is high (approximately $3,000 USD/day), large-scale, multicenter studies are needed to better define the congenital heart population most likely to experience long-term benefit [292]. A recent review of children undergoing heart surgery who did and did not have pulmonary hypertension found that administration of iNO after pediatric cardiac surgery increases length of stay and billed charges, while not providing improved inpatient mortality in either group, and may be detrimental to those without pulmonary hypertension [293].

Toxicity of iNO is very low at clinically relevant concentrations. Methemoglobinemia is a potential problem if high doses (>80 ppm) are administered for an extended time, or for patients with genetic deficiency of methemoglobin reductase. Peroxynitrite results from the reaction of nitric oxide with superoxide and is a potent oxidant and pulmonary irritant. In high concentrations, peroxynitrite can damage DNA, induce apoptosis, and impair the vasorelaxant function of endothelium [294]. iNO also increases ET-1 secretion, which may account for some of the rebound pulmonary hypertension observed when iNO is discontinued [295].

Nitric oxide donors and precursors have been employed in the treatment of increased PVR in the postoperative setting. Nitric oxide is a product of arginine, an amino acid in the urea cycle. Since low levels of urea cycle intermediates have been observed in CHD patients following CPB, investigators have successfully prevented postoperative pulmonary hypertension in children by supplementation with both oral and intravenous citrulline, lending further evidence to the pivotal role of the pulmonary endothelium [296–298]. Nitroglycerin is a potent nitric oxide donor with a very short half-life and has been useful in pediatric cardiac surgery [299]. However, nitroglycerin is a nonspecific vasodilator and preferentially dilates the venous circulation, potentially leading to decreased preload and decreased cardiac output.

Inhaled epoprostenol (prostacyclin) is a prostaglandin analog with nonspecific vasodilating properties. It acts via specific membrane receptors to increase intracellular cAMP and, therefore, activate cAMP-dependent protein kinases. Long-term management of pulmonary hypertension, related or unrelated to CHD, often involves intravenous infusion of epoprostenol. Prostacyclin has shown efficacy for both adults and children with pulmonary hypertension related to CHD [284, 300, 301]. Inhaled prostacyclin shares the advantage of iNO, in that both treatments are very selective for the pulmonary vasculature and have little, if any, effect on systemic vascular resistance. In the post-transplant cardiac surgery population, a large randomized trial found no difference in efficacy between iNO and prostacyclin [302]. In an uncontrolled case series of post-CPB pediatric patients, inhaled prostacyclin was effective at decreasing pulmonary pressure, but one-third of the subjects required norepinephrine as a systemic vasoconstrictor agent, indicating that this agent is somewhat less selective for the pulmonary vasculature than iNO [303].

PDEIs represent another pharmacological approach to increased PVR. These agents increase the intracellular levels of cyclic nucleotides (cAMP and cGMP) by inhibiting enzymes responsible for their breakdown. PDEIs selective for PDE-5 inhibit breakdown of cGMP and are therefore vasodilatory, with sildenafil being the agent in most frequent clinical use. Sildenafil has been useful for managing both idiopathic pulmonary hypertension and pulmonary hypertension associated with CHD in children [304]. In laboratory models of pulmonary hypertension, PDEIs have shown efficacy both alone and in combination with other agents [305, 306]. Because of their favorable safety profile, PDEI use has expanded, especially in the pediatric population [307–311]. However, the quality of the evidence for many of these studies is suboptimal, relying on retrospective associations and prospective studies with small sample size or in limited populations, making it difficult to extrapolate their findings to other populations or practices.

ET-1 is a vasoconstrictive peptide released from endothelium. In the pulmonary circulation, ET-1 binds to specific ET(A) receptors on smooth muscle and initiates protein kinase C activation and increased intracellular calcium levels, producing vasoconstriction. Specific ET(A) receptor antagonists have been effective for the treatment of pulmonary hypertension, specifically in the post-CPB setting [312, 313]. As in the case for PDEIs, ET(A) receptor antagonists were first used in outpatients for the management of idiopathic pulmonary hypertension, and their clinical application expanded from there into the cardiac surgery, transplant, and ICU settings [300, 314–318]. Also, as in the case for PDEIs, extrapolation of the findings from many of these studies may be hampered by small sample sizes and lack of appropriate controls.

MUF is a nonpharmacologic technique that has multiple salutary effects on pediatric organ systems in the post-CPB period [319]. Most of the pulmonary benefits of MUF appear to result from improved hemodynamics (vascular tone, ventricular function) and decrease in lung edema. MUF in animal models decreases pulmonary resistance [320]. MUF in a study of infants with transposition of the great arteries and in a mixed population of CHD showed improved oxygenation and hemodynamics [321, 322]. Bando et al. identified neonates and patients with preoperative pulmonary hypertension as a specific subgroup that experiences greater benefit from MUF, albeit in a noncontrolled, retrospective analysis [48].

CPB and lung parenchyma

The compromised state of gas exchange for infants and small children is further impaired after CPB. Lung injury in this setting arises from several concurrent insults: the inflammatory response to CPB, oxidative pulmonary injury, loss of surfactant production, increased lung edema, atelectasis, and loss of lung volumes. As any pediatric intensive care practitioner can attest, the inability to separate from mechanical ventilation is a major contributor to prolonged ICU stay [259].

Pulmonary capillary leak following CPB produces accumulation of interstitial lung water, which is the central pathophysiologic process mostly responsible for impaired gas exchange and decreased pulmonary compliance. Although some pulmonary edema occurs in nearly all patients, a small fraction of patients experience respiratory distress syndrome following CPB, characterized by severe lung edema, and an associated high morbidity and mortality [323]. As mentioned

in detail in the previous section, CPB activates neutrophils, which then translocate across pulmonary capillaries. Once in tissues, activated neutrophils release free radicals and proteolytic enzymes, which further disrupt the integrity of the pulmonary capillaries [324, 325]. Pulmonary ischemia and reperfusion also contribute to impaired postoperative ventilatory function. Reduced ventilation and decreased total lung compliance correlate significantly with markers of oxidative injury in infants following cardiac surgery [326].

Deflation of the lungs during CPB produces large areas of atelectasis, and accumulation of secretions can prolong airway collapse and loss of lung volumes. These effects are magnified in small infants, where decreased pulmonary surfactant production may be further impaired by CPB [327, 328]. Accumulation of blood or fluid in the pleural spaces, or the presence of chest tubes or other devices, can contribute to lobar or segmental collapse.

Transfusion-related acute lung injury (TRALI) occasionally complicates the postoperative course of children with CHD. TRALI is often a diagnosis of exclusion, being an uncommon cause of pulmonary edema. Because TRALI is most likely caused by donor antibodies directed against recipient leukocytes, plasma is often the cause, although identity of the offending blood unit is not part of the case definition [329]. In pediatric cardiac surgery, transfusion of blood products is significantly associated with postoperative morbidity, including pulmonary complications, but it is unclear what role immunologically identified TRALI may have in this association, and to what extent blood transfusion is simply a marker for case complexity. TRALI appears to be less common in children than in adults, although part of this observation may be a result of under-reporting or under-recognition [330].

Techniques to improve respiratory function

Multiple strategies have been proposed for improving gas exchange and lung compliance; these largely focus on controlling two processes: reduction of lung water and prevention of atelectasis [331, 332].

As pulmonary edema is a result of inflammation, reperfusion, and oxidative injury, efforts to control or reduce pulmonary edema have focused on these pathophysiologic processes. Although activated neutrophils directly disrupt the pulmonary capillary barrier, leukocyte depletion of circulating blood has shown modest or inconsistent results and depends significantly on the population being studied [333–335]. Leukocyte depletion has been reported for the CPB pump prime, residual pump blood, or continuous leukofiltering during CPB [336–342]. Interestingly, improved respiratory function has been achieved in this setting with the use of neutrophil elastase inhibitors [343]. Many of these studies report data from experimental animal models or adult patients; therefore, extrapolation to children may not necessarily be valid, although one author has identified children as a population most likely to benefit [335].

Pulmonary perfusion during CPB avoids reperfusion injury, and therefore, lung edema, by omitting a period of lung ischemia. Apparently bronchial circulation is insufficient alone to meet metabolic demands of the lung for a sustained period of time. Lung water and markers of inflammation can be significantly attenuated by pulmonary perfusion during CPB, either with blood or with a protectant solution [10, 11, 272, 344, 345]. Improved oxygenation is also achieved by maintaining lung perfusion during CPB.

Pulmonary injury and dysfunction resulting from TRALI can be prevented by minimizing transfusion, especially of plasma and cryoprecipitate. Efforts to optimize blood transfusion are discussed earlier in this chapter. Supportive care is the mainstay of treatment, consisting of oxygen supplementation, noninvasive or invasive ventilation, positive end-expiratory pressure (PEEP), and diuresis [346]. Notification of the blood bank is prudent when TRALI is suspected, as donor identification may prevent future cases [347].

MUF, mentioned previously for its benefits in attenuating pulmonary vasoreactivity following pediatric CPB, has shown benefit for the removal of lung water, resulting in increased lung compliance and improved gas exchange, with the effect being most notable within the first 6 hours postoperatively [348–352]. MUF also decreases the duration of mechanical ventilation following congenital heart surgery, with the youngest infants most likely to benefit [353–355].

Atelectasis in small infants is often due to deficient or dysfunctional surfactant. Surfactant is a physiologic necessity for maintaining airway and alveolar patency during ventilation, and CPB has deleterious effects on measures of surfactant activity [301, 302, 331, 332]. A retrospective study of exogenous surfactant for infants with respiratory distress syndrome after cardiac surgery reported an improvement in oxygenation index and shorter duration of mechanical ventilation and hospital stay when compared with historical controls [356]. Other authors have reported benefits of pulmonary surfactant supplementation in children with CHD during ECMO or in respiratory distress outside the perioperative period [357–359].

Optimization of mechanical ventilation parameters in the post bypass period is critical in maintaining oxygenation and ventilation, but attention should also be given to the effects on cardiopulmonary interactions and pulmonary vascular resistance. Ventilation at or near FRC results in the lowest PVR. Volumes below FRC lead to atelectasis, while higher volumes lead to pulmonary vessel compression, thus increasing PVR. While most advocate for a lung-protective strategy of lower tidal volumes and optimal PEEP, this must be balanced with the specific cardiac physiology and how mean airway pressure will affect preload and afterload [360].

For surgeries at risk for postoperative pleural effusions, and the Fontan in particular, there is recent evidence that management protocols may reduce duration of pleural drainage and hospital stay [361, 362]. These protocols typically include a combination of pharmacologic therapies including anticoagulation, fluid and dietary management, and respiratory therapy, which may or may not be initiated in the operating room [363, 364].

The routine practice of suspending ventilation during CPB results in near-total atelectasis by the end of CPB. Recruitment of collapsed alveoli and maintenance of ventilation are necessary for separation from CPB. While a sustained inflation (recruitment maneuver) alone is probably ineffective for maintaining open alveoli, it can effectively prevent atelectasis well into the postoperative period when followed by maintenance of PEEP [365, 366]. But these findings are based on adult data and have not been duplicated in children.

However, a randomized study of dornase alpha (a mucolytic agent) after pediatric CPB reported significantly improved radiographic atelectasis scores and oxygenation as compared with controls receiving chest physiotherapy [367].

KEY POINTS: PULMONARY EFFECTS OF CONGENITAL HEART SURGERY

- Ventilation in infants is physiologically compromised, compared with older children.
- PVD results from increased pulmonary blood flow, causing increased vascular resistance, increased sensitivity to vasoconstrictor stimuli, and histologic changes.
- Multiple factors increase PVR following CPB: ischemia–reperfusion injury, endothelial dysfunction, and preexisting PVD.
- Management of post-CPB PVR is with vasodilators: iNO, prostanoids, and PDEIs.
- The direct effects of pulmonary capillary leak are decreased pulmonary compliance and decreased gas exchange.
- Avoidance of ischemia–reperfusion, use of MUF, and recruitment of atelectatic lung segments decrease clinical impact of pulmonary capillary leak.

Renal effects of congenital heart surgery

Introduction, incidence, and definition of the problem

Renal injury is a well-known complication of the surgical management of CHD. Depending on the outcome definition, and the population under study, acute kidney injury (AKI) affects up to 64% of children requiring CPB [368–370]. The incidence is difficult to quantify accurately due to the range of definitions of acute renal failure (ARF) and significant institutional variability in the institution of renal replacement therapy [371, 372]. The kidneys are exposed to a range of insults associated with the surgical management of CHD and renal injury is thought to be the result of hypotension, systemic inflammatory response, and perioperative use of nephrotoxic medications [368, 369, 373].

Several studies have identified perioperative factors that increase the risk to the kidney. Younger age, smaller size, duration of CPB and aortic cross-clamp, intraoperative transfusion, early postoperative hypotension, 24-hour postoperative lactate levels, duration of mechanical ventilation, and vasopressor use have all been associated with renal injury [368, 370, 372–375]. Genetic factors have also been identified [376]. Renal injury co-associates with many risk factors for postoperative low cardiac output syndrome (LCOS), so the association of renal injury with inotropic support may represent an epiphenomenon. The PRIMACOR study, in fact, found no independent association of reduced postoperative creatinine clearance with the use of milrinone [377]. In a retrospective study examining the risk of ARF after cardiac surgery preceded by cardiac catheterization, young age, amount of iodinated contrast received, and the presence of LCOS were identified as risk factors. Age less than 2 years was associated with a 20-fold increase in the risk of perioperative AKI in children who underwent preoperative cardiac catheterization [378].

Younger children are particularly prone to renal injury, as the kidney of an infant functions less effectively until approximately 2–3 years of age [379]. Infants have decreased glomerular filtration rate (GFR) due to increased renal vascular resistance in the setting of low mean arterial pressure. When decreased GFR is considered in the setting of immature tubular cell function, tubular reabsorption is substantially impaired when compared with adult patients. Given that many challenging cardiac operations occur in the newborn period, it is little surprise that an increased incidence of renal dysfunction is seen in the youngest patients, independent of immature renal function.

One operational cause of our inability to understand or predict the occurrence of AKI following congenital heart surgery has been the lack of a consistent definition of AKI across studies. In 2001, the Acute Dialysis Quality Initiative Group proposed the adult RIFLE (risk, injury, failure, loss, and end-stage renal disease), which aimed to standardize the definition of AKI and stratify kidney injury based on the degree of elevation of serum creatinine, decrease in estimated GFR, or prolonged oliguria. The pediatric modification of the RIFLE score (pRIFLE) detects acute renal injury in critically ill children and is a predictor of length of stay and mortality, independent of the Pediatric Risk of Mortality (PRISM) score [380, 381]. Pediatric RIFLE scoring stratifies renal dysfunction based on reduction in estimated creatinine clearance, elevation in serum creatinine above baseline, or reduction in urine output (Table 12.5). The Acute Kidney Injury Network (AKIN) has devised a similar score, the AKIN score, which appears to correlate well with pRIFLE [369, 380]. Late renal failure (pRIFLE categories L and E), however, remains difficult to define in the postoperative congenital cardiac population, due to wide variation in postoperative use of peritoneal dialysis (PD) [382]. Small increases in serum creatinine in the early postoperative period predict kidney injury using the pRIFLE criteria, and more severe renal injury predicts worse clinical outcomes. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) classification systems integrated the pRIFLE and AKIN classification systems. Importantly, while progress has been made in the staging and characterization of renal dysfunction, many studies also vary in their postoperative observation window, accounting for some variability in reported incidence. In comparing the various scoring systems, pRIFLE is more sensitive for the detection of mild degrees of renal dysfunction, KDIGO is applicable to both adult and pediatric patients and does not limit the diagnostic time frame, and AKIN does not require knowledge of the patient's height or baseline creatinine clearance. KDIGO is thought to be the most inclusive classification of renal injury by those investigators who focus in this area [383] (Table 12.5).

Emerging biomarkers of renal dysfunction

Serum creatinine is most commonly used to estimate GFR, the volume of filtrate entering the renal tubules at the glomerulus per unit of time. Estimates of GFR using serum

Table 12.5 Staging of acute kidney injury in children

AKI staging	Criteria – eGFR or SCr	Criteria – urine output (UOP)
pRIFLE		
Stage 1 (Risk)	eGFR decreased by 25%	UOP < 0.5 mL/kg/hour for 8 h
Stage 2 (Injury)	eGFR decreased by 50% eGFR decreased by 75%	UOP < 0.5 mL/kg/hour for 16 h
Stage 3 (Failure)	Persistent failure >4 weeks	UOP < 0.3 mL/kg/hour for 24 h or anuria >12 h
Stage 4 (Loss)	ESRD, Persistent failure >3 months	
Stage 5 (End-stage)		
AKIN		
Stage 1	SCr increased by 50% or 0.3 mg/dL	UOP < 0.5 mL/kg/hour for 6 h
Stage 2	SCr increased by 100%	UOP < 0.5 mL/kg/hour for 12 h UOP < 0.3 mL/kg/hour for 24 h or anuria >12 h
Stage 3	SCr increased by 200%	
KDIGO		
Stage 1	SCr increased by 50% or 0.3 mg/dL	UOP < 0.5 mL/kg/hour for 6–12 h
Stage 2	SCr increased by 100%	UOP < 0.5 mL/kg/hour for > 12 h
Stage 3	SCr increased by 200% or eGFR <35 mL/min/1.73 m^2 (age <18 years)	UOP < 0.3 mL/kg/hour for 24 h or anuria >12 h

AKIN, Acute Kidney Injury Network; eGFR estimated glomerular filtration rate (estimated using the Schwartz method); ESRD, end-stage renal disease; KDIGO, Kidney Diseases Improving Global Outcomes; pRIFLE, pediatric RIFLE; SCr, serum creatinine; UOP, urine output.

creatinine measurements may be insensitive indicators; serum creatinine often does not rise until GFR falls below 80 mL/min/1.73 m^2. Because creatinine is also secreted by the proximal tubule, GFR may be reduced by up to 50% before elevations in serum creatinine are observed [384].

There is substantial interest in other potential indicators of renal dysfunction, which are more sensitive to declining GFR, and reflect renal function in real time. Biomarkers are often studied in children undergoing cardiac surgery as most pediatric patients lack significant renal comorbidities and the time of the renal insult is relatively well defined. These biomarkers offer the potential ability to detect tubular injury prior to a rise in serum creatinine or a reduction in urine output. Cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) are the two markers in clinical use today.

Cystatin C is a cysteine protease inhibitor produced by nucleated cells throughout the body at a constant rate. It is filtered at the glomerulus and not secreted by tubules, and its levels are independent of gender, muscle mass, and fluid overload. Normal levels of cystatin C are somewhat higher in neonates and small infants (Figure 12.7) [385]. Serum cystatin C levels show stronger correlation with measured GFR than do serum creatinine levels in young children and adolescents [386]. Cystatin C has emerged as a highly sensitive indicator of renal dysfunction in children following cardiac surgery, and serum elevation of cystatin C occurs within hours of injury to the kidney (Figure 12.8) [386–388]. Cystatin C concentrations correlate with the severity of AKI (defined by pRIFLE criteria) beginning 2 hours after CPB. Interestingly, half of the patients included in this study were less than 2 years of age. The first postoperative cystatin C levels and the postoperative cystatin C changes from baseline value were independently associated with duration of mechanical ventilation in this study, whereas serum creatinine levels were not [387].

NGAL is a marker of tubular injury and its levels rise early following a given insult and levels correlate both with the degree and severity of AKI [389, 390]. The diagnostic utility of NGAL in AKI has been reviewed extensively [391]. Because NGAL is useful in risk prediction, NGAL levels have been used as a measure of renal injury in clinical trials. The ability to detect renal tubular injury that does not result in an increase in serum creatinine makes NGAL a useful measure of subclinical AKI. In studies of both adult and pediatric patients, NGAL elevation in the absence of increased creatinine was associated with a two- to three-fold increase in risk of death or dialysis [392].

Association of renal injury with clinical outcomes

In adult cardiac surgery, even mild renal dysfunction is associated with greater length of hospital stay, cost, and mortality. It is unclear to what degree these associations also exist for children. Many authors have studied this question using retrospective data and have reported associations between

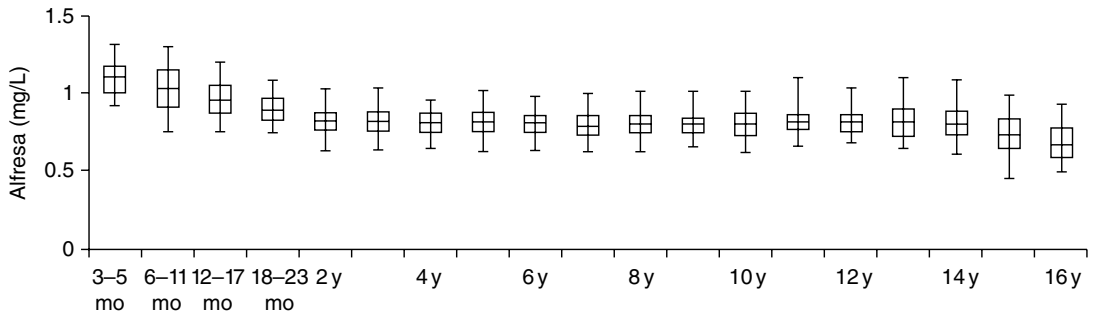


Figure 12.7 Serum cystatin C in children aged 3 months (mo) to 16 years (y). The box plot extends from the 25th percentile to the 75th percentile, with the horizontal line at the median, and the whiskers show the central 95% of the data for the Alfresa assay. (Source: Yata et al. [357]. Reproduced with permission of Springer Nature.)

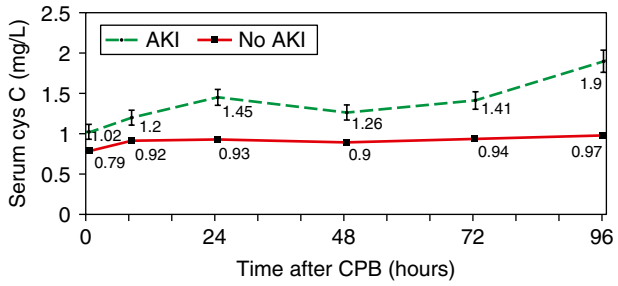


Figure 12.8 Serum cystatin C levels in patients with and without acute kidney injury (AKI) over the study period. Cystatin (cys) C levels displayed as least square means (±SE). *P*-values obtained using differences of least square means after Tukey–Kramer adjustment.* *P*-value <0.05. (Source: Hassinger et al. [360]. Reproduced with permission of Wolters Kluwer Health, Inc.)

poor clinical outcomes and mild renal dysfunction. Some studies, however, are small or do not control for sufficient covariates.

Although some studies do suggest that subclinical AKI may portend significant clinical consequences for children, it is clear that the more severe forms of perioperative AKI are significant harbingers of poor outcome. Tóth et al., using propensity-matching, observed AKI in 32% of patients, with 11.5% meeting criteria for risk, 1.7% for injury, and 18.7% for failure by pRIFLE [393]. They further reported an association between AKI, increased length of ICU stay, and mechanical ventilation, but not in-hospital mortality in their 1,510 patient cohort. Morgan et al. studied the neonatal population for a follow-up of 2 years and found AKI in 64% of subjects, as defined by AKIN criteria. AKI was associated with duration of mechanical ventilation, length of ICU stay, and length of hospital stay after accounting for covariates by regression [370]. They observed an increase in 2-year mortality in patients with AKIN stage 2 or higher [370, 394]. In a retrospective cohort of 409 children undergoing congenital cardiac surgery, early AKI by pRIFLE criteria was observed in 20% of subjects and was associated with length of ICU stay, duration of mechanical ventilation, and mortality [395]. In another retrospective cohort of 693 postoperative cardiac patients, investigators observed a 15% incidence of AKI (11% mild, 3% moderate, 1% severe), by AKIN criteria. These investigators observed that only moderate and severe AKI were associated with prolonged postoperative recovery [375].

Renal failure and renal replacement therapy following cardiac surgery in children

The use of renal replacement therapy for postoperative renal failure is difficult to determine given the wide variability in practice patterns across institutions. In patients with severe hemodynamic instability, continuous veno-venous hemofiltration (CVVH) may provide the optimal means of renal replacement therapy. Most patients, however, will tolerate the initiation of PD as a means of augmenting the function of failing kidneys, as a method of avoiding volume overload, or as a means of modulating the inflammatory response seen post-CPB in these children. Duration of AKI prior to the initiation of renal replacement therapy was associated with increased mortality in children following cardiac surgery [396, 397].

Peritoneal dialysis

PD is frequently used in postoperative management of patients following cardiac surgery. Although initial application in this population was intended for the management of postoperative renal failure, its indications have expanded to include fluid overload, optimization of cardiac loading conditions, decompression of the abdominal cavity, and mitigation of the inflammatory sequelae of CPB. Peritoneal drainage catheters (PDCs) can be used as either a passive drain in the abdominal cavity or a means of initiating PD for active fluid and electrolyte management. An analysis of data from 2006 and 2009 in the Kids' Inpatient Database in this population found that young age, higher Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, ARF, CPB, nonelective admission, and hospital region in the south or west were associated with increased rates of PD catheter placement. There is widespread variability in the indications and frequency for PD in pediatric cardiac surgical patients across institutions, although those patients undergoing PDC placement represent a relatively high-risk subset within the postoperative population [382].

PD carries some risk. In a review of 1,128 patients undergoing congenital cardiac surgery who underwent PDC placement, 130 developed complications. Most events were minor and included leakage and mechanical dysfunction, 6.2% developed severe complications (hydrothorax, hemoperitoneum, bowel perforation, and peritonitis). However, mortality in patients with PD complications was not significantly different than those without PD complications [398].

PD in the management of postoperative fluid overload

Fluid overload is often seen in young patients following CPB. As outlined extensively in this chapter, capillary leak associated with CPB, transfusion, administration of crystalloid, myocardial dysfunction, and activation of the renin–angiotensin–aldosterone system all contribute to postoperative fluid overload. Reduced GFR and medullary concentrating ability in young children also predispose to fluid overload. Fluid overload can delay sternal closure, prolong duration of mechanical ventilation, and limit the ability of the GI tract to process enteral nutrition properly. Fluid overload as measured by daily weight is associated with worse clinical outcome among infants undergoing cardiac surgery [399].

The use of PDCs allows for the safe and effective removal of fluid during the postoperative period. It improves early postoperative hemodynamics and ICU outcomes [400–402]. In two different observational studies of children undergoing congenital cardiac surgery, early PD was associated with a significantly negative fluid balance [402, 403]. In a 2017 study, infants who were oliguric in the early postoperative period were randomized to furosemide or PD. Those who underwent PD were three times less likely to develop fluid overload and less likely to require postoperative mechanical ventilation. They did not find, however, a reduction in time until delayed sternal closure, duration of mechanical ventilation, hospital length of stay, or mortality [404, 405].

PD for the mitigation of the systemic inflammatory response

PD can mitigate the inflammatory response to CPB. In congenital heart surgery, serum IL-6 levels have been associated with AKI and duration of mechanical ventilation, and PD removes pro-inflammatory cytokines IL-6 and IL-8 [406, 407]. In an observational study comparing passive peritoneal drainage and diuresis with PD, the latter was associated with earlier sternal closure (24 vs. 63 hours), lower mean inotropic scores, shorter duration of mechanical ventilation (71 vs. 125 hours), and greater net negative fluid balance [408]. A propensity-matched study compared early (within 6 hours of CPB) or late initiation of PD and found substantial reduction in adverse events in the early PD initiation group. The decision to initiate PD was at the discretion of the patient's care team [409]. This area would most certainly benefit from randomization of patients in more highly protocolized trials to further clarify the potential benefits of this intervention.

Continuous veno-venous hemofiltration

Hemodialysis allows for volume and solute management using ultrafiltration and diffusion across a semi-permeable membrane. When done intermittently, it results in rapid shifts of solute and solvent, and a large extracorporeal volume burden, which makes it an unpopular choice in the postoperative population. CVVH is thought to be a better-tolerated means of volume management used in postoperative cardiac surgery patients. Anticoagulation is necessary to maintain patency of CVVH systems, and complications can arise related to vascular access for CVVH. In the event that more aggressive solute clearance is required, continuous veno-venous hemodialysis may be required, in which case dialysis fluid is introduced into the hemofiltration cartridge, which increases electrolyte clearance. Hypokalemia is frequently seen during this procedure, and potassium may be added to the dialysis solution to avoid this complication.

KEY POINTS: RENAL EFFECTS OF CONGENITAL HEART SURGERY

- Impaired renal function is common after bypass and is most frequent and severe in infants undergoing complex operations.
- Studies of perioperative renal injury in children are contradictory because of differences in end point definition and monitoring windows.
- Perioperative renal injury is associated with poor clinical outcomes – duration of mechanical ventilation, length of ICU and hospital stay, and mortality – with worse injury associated with worse outcome.
- Use of PD can improve early postoperative hemodynamics, but not necessarily mortality or other long-term outcomes.
- Continuous veno-venous hemodialysis is a form of renal replacement therapy which can avoid rapid fluid and solute shifts associated with intermittent dialysis.

GI and hepatic consequences of cardiac surgery in children

Splanchnic circulation

Mesenteric Ischemia and NEC

Bowel ischemia has been reported in adults following CPB [410–413]. Reported risk factors include age, atherosclerosis, heart failure, renal failure, use of vasoconstrictors, prolonged mechanical ventilation, and use of intra-aortic balloon counterpulsation [412, 414–416]. Reports of mesenteric ischemia are very rare in the pediatric population. The single exception is gut ischemia seen after use of intra-aortic balloon pumps [417, 418].

NEC is a common and devastating disease in the neonate. The pathogenesis of NEC is not clearly defined and is likely multifactorial with a complex interplay of altered intestinal microbiota, genetic polymorphisms, an immature intestinal barrier, and an exaggerated inflammatory response [419]. Primarily a disease of the premature infant, especially those with very low birth weight (i.e. <1,500 g), 10% of infants affected are term or near-term neonates [420]. The incidence of NEC in the neonate with CHD ranges from 2.5 to 7.8%, and this population accounts for most of the term infants with the disease [420–425]. In a large, retrospective analysis of term infants with CHD, McElhinney et al. found that diagnosis of hypoplastic left heart syndrome, truncus arteriosus, and aortopulmonary window were independently associated with NEC, with hypoplastic left heart syndrome conveying the highest risk [425]. In the Single Ventricle Reconstruction trial examining 549 neonates with single ventricle physiology across 15 centers, the incidence of NEC was 2.5% as defined by pneumatosis intestinalis or free air on radiographs [426]. In a retrospective study of neonates who underwent a hybrid procedure (bilateral pulmonary artery banding, ductal stenting, possible atrial septal stent), the incidence of NEC was 11%, but neonates who developed NEC were significantly younger than hybrid neonates who did not develop NEC [423].

NEC in the neonate with CHD may be a distinct disease process from that in the neonate without CHD. Vascular insufficiency rather than gut immaturity could be the underlying cause of bowel ischemia in this population. Episodes of hypoperfusion, shock, and diastolic flow reversal in the aorta and superior mesenteric artery have been associated with NEC in the CHD population [427–431]. Mechanisms of intestinal ischemia may be related to physiologic steal that can occur in a parallel circulation. Clinical presentation tends to occur earlier in the neonate with CHD. In a retrospective look at 202 CHD patients with NEC, 48% were diagnosed before medical or surgical intervention on the cardiac lesion [432]. In the CHD population, NEC lesions are typically found in the colon, as opposed to lesions in children without CHD where the jejunum and ileum are most often affected [433]. Several studies have found that infants with CHD had decreased risk of perforation, strictures, need for a stoma, sepsis, and short gut syndrome compared with infants without CHD [425, 432, 434, 435]. While mortality in neonates with CHD and NEC does not appear to be higher than that of cardiac neonates without NEC, morbidity is adversely affected. The diagnosis of NEC extends critical care and hospital length of stay significantly and increases the financial burden of care by $95,600–$316,000 [436–438].

Although a great deal has been learned about the pathogenesis of NEC, progress with respect to prevention and early detection has been slow, with radiographic imaging still the current standard. Gastric tonometry, abdominal ultrasound/Doppler, and a variety of biomarkers have not been successful in the early detection or prevention of NEC. Near-infrared spectroscopy (NIRS), a noninvasive technology that measures regional oxygen saturation, has been investigated as an early warning device for evolving tissue hypoxia. In 2011, Gay et al. described how abdominal NIRS probes were able to rapidly detect changes in mesenteric blood flow in an animal model of NEC [439]. A number of case reports describe changes in abdominal NIRS values in neonates with NEC [440, 441]. In an interesting study by Fortune et al., the authors found that the cerebral–splanchnic oxygen ratio (CSOR) could be more predictive of abdominal pathology than splanchnic NIRS alone. The authors demonstrated that a CSOR value of less than 0.75% predicted splanchnic ischemia with a positive predictive value of 0.75 and a negative predictive value of 0.96 [442].

In summary, neonates with CHD are at increased risk for NEC. Mortality does not appear to increase with this diagnosis in the CHD population, although hospital and critical care unit length of stay is prolonged. NIRS shows promise as a tool for early prediction of mesenteric ischemia, but further investigation is needed.

Hepatic dysfunction

Acute hepatic failure has been described in the postoperative course of infants and children following cardiac surgery, but the relationship to the intraoperative course is uncertain. In a prospective observational study of 232 patients at a single institution, liver dysfunction was noted in 9.3% of patients, as defined by a scoring system calculated using alanine amino transferase, total bilirubin, and prothrombin time. Shock in the postoperative period was the most important predisposing factor for hepatic dysfunction [443]. Previous retrospective studies link low cardiac output and elevated right atrial pressures as risk factors for hepatic failure [444, 445].

Authors reviewed 16 cases of acute hepatic failure in the setting of MSOF in children after cardiac surgery at a single institution spanning a 4-year period. Over this time period, 3.5% of patients developed MSOF in the postoperative period. All patients underwent surgical correction using either deep hypothermic cardiac arrest (DHCA) or low-flow CPB (25% of initial flows). DHCA was always less than 60 minutes at 16 °C. Duration of low-flow CPB was not described. Hepatic failure occurred in all 16 patients as defined by a serum glutamic oxaloacetic transaminase (SGOT) >500 IU/L and a prothrombin time prolonged by at least 50%. SGOT values decreased after 48 hours in both survivors and nonsurvivors and normalized by 1 week in all survivors. Central venous pressures ranged, respectively, from 3 to 17 mmHg and 8 to 17 mmHg at 4 and 24 hours postoperatively. Hepatic perfusion pressures ranged, respectively, from 35 to 67 mmHg and from 21 to 66 mmHg at 4 and 24 hours postoperatively. The most striking aspect of the perioperative course was the dose of epinephrine used. Doses ranged from 0.05 to 1.19 μg/kg/min with a mean of 0.43 μg/kg/min and were administered for a poorly contracting myocardium [446] There are anecdotal reports of hepatic failure and MSOF following cannula malposition of the inferior caval cannula in bicaval cannulation for CPB.

Effects of chronically elevated systemic venous pressure

While the Fontan palliation results in a near-normal systemic arterial saturation, elevated systemic venous pressure results. Because portal venous blood comprises 75% of hepatic arterial blood flow, normal blood flow within the liver is dependent upon portal venous pressure exceeding that of the hepatic vein draining the liver parenchyma. The GI system in particular is vulnerable to the adverse consequences of chronic elevations in systemic venous pressure by virtue of its reliance on a pressure gradient between two low-pressure venous systems in series. In the setting of reduced cardiac output for any reason, blood flow is diverted away from the GI tract in favor of the cerebral and coronary systems. Chronic liver injury in these patients is the expected consequence, and care of these patients should include regular monitoring of hepatic function. Protein losing enteropathy (PLE) is another potentially devastating consequence of the Fontan circulation, though its consequences may be more severe. Although its etiology is not clearly understood, chronic elevations in systemic venous pressure resulting in increased lymphatic pressure is thought to result in protein loss in the GI tract [447].

Chronic elevations in systemic venous pressure and hypoxemia result in dilatation of hepatic sinusoids and hepatocyte necrosis and may progress to varying degrees of fibrosis of the tissues adjacent to the hepatic veins. This fibrosis may progress to cirrhosis. As the body begins to compensate for reductions in portal venous flow by increasing the arterial component of hepatic blood flow, focal nodules of hepatocyte regeneration may result [448, 449].

Feeding and nutrition

Feeding difficulties and weight gain are commonly seen in children with CHD. Poor oral feeding, intolerance of enteral feeds, and an increased risk of NEC all complicate the recovery of many neonates and infants following cardiac surgery. Vocal cord dysfunction, prolonged need for narcotic or sedative infusions, prolonged mechanical ventilation, oropharyngeal aspiration, and intestinal ischemia have all been postulated to be contributory. Need for prolonged mechanical ventilation was associated with an increased time to full enteral feeds and was also associated with the need for nonoral feeds at the time of discharge [450]. In a single-center study of patients undergoing surgical gastrostomy following cardiac surgery, the authors found a higher incidence of feeding intolerance in cardiac surgical patients (18.8 vs. 5.6% in noncardiac surgical patients) and a longer time to achieve full enteral nutrition targets. In this cohort, 58% of children were able to wean from gastrostomy tube feedings by 12 months following placement [451].

A retrospective analysis of data from the National Pediatric Cardiology Quality Improvement Collaborative data registry examined the data from patients who underwent Stage 1 palliation of hypoplastic left heart syndrome from 2008

to 2016 was examined to determine factors associated with feeding outcomes. Factors associated with increased time to full enteral feeding included earlier gestational age, need for arch reintervention, multiple repeat procedural interventions, and GI anomaly [452]. Some studies have shown that the use of institutional feeding protocols has been correlated with decreased time to full enteral feeds and with decreased rates of NEC, but other studies have been unable to demonstrate this [453, 454].

Endocrine response and pediatric cardiac surgery

Critical illness-related corticosteroid insufficiency

The acute stress response to critical illness and surgical stress is the result of activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathoadrenal system. During stress, the HPA axis typically responds by enhancing the release of cortisol (Figure 12.9). Approximately 85% of cortisol in the circulation is bound to corticosteroid-binding globulin (CBG) and 10% is bound to albumin. The remaining portion, free cortisol, is thought to be that which is biologically active [455]. Cortisol exerts its effects by binding to intracellular glucocorticoid receptors, which play an important role in glucose metabolism, adrenergic receptor function, maintenance of endothelial integrity, and the systemic inflammatory response. CBG serves as a reservoir for protein-bound cortisol and is increasingly thought to play a role in facilitation of the activities of cortisol [456]. In critical illness, the HPA response to stress may be inadequate and result in persistent and profound inflammatory processes and hemodynamic insufficiency. It may result from either inadequate adrenal steroid production or decreased peripheral sensitivity to glucocorticoids. This dysfunction of the HPA axis in critical illness is usually temporary, can occur without structural insult to the hypothalamus, pituitary, or adrenal glands, and is termed critical illness-related corticosteroid insufficiency (CIRCI).

Diagnosis of CIRCI

CIRCI, also known as relative adrenal insufficiency, has been defined as an inadequate level of serum cortisol relative to the severity of the patient's illness and has been hypothesized

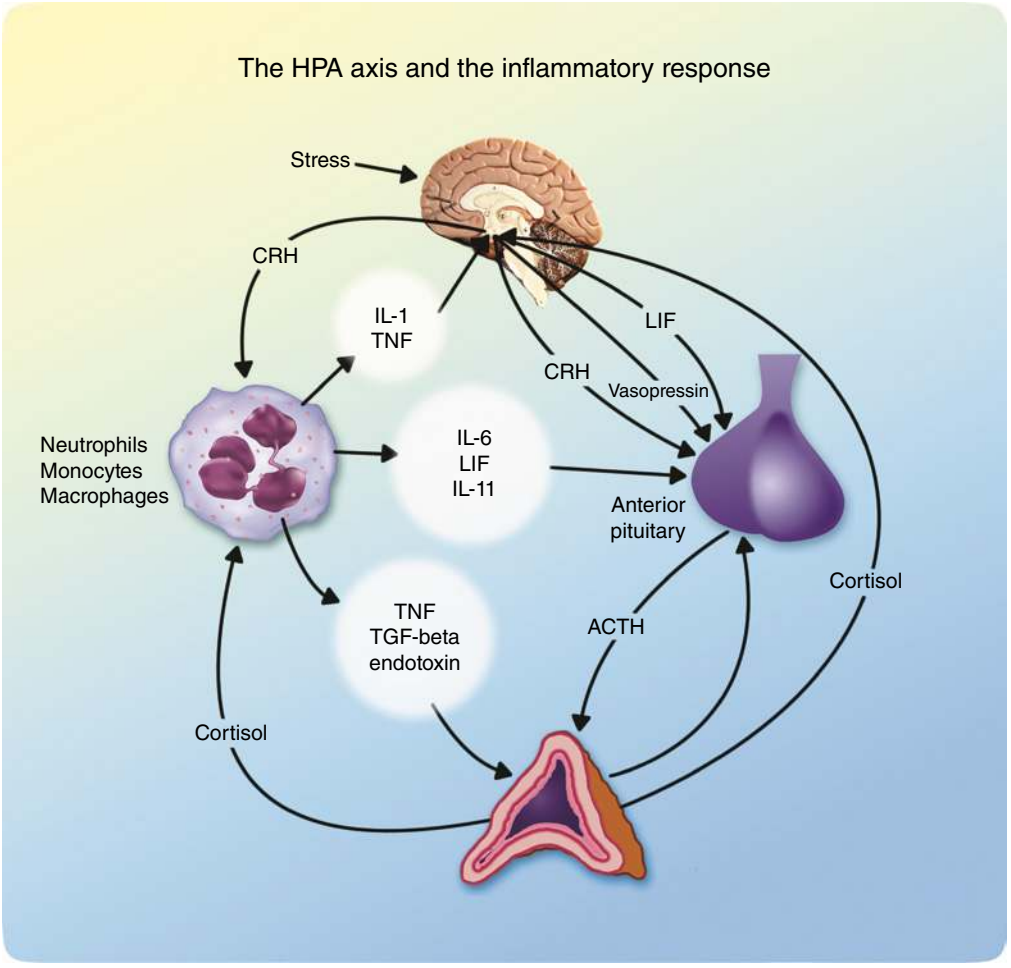


Figure 12.9 Activation of the hypothalamic–pituitary–adrenal (HPA) axis by a stressor and the interaction with the inflammatory response. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; IL-6, interleukin-6; IL-11, interleukin-11; LIF, leukemia inhibitory factor; TGF-beta, transforming growth factor-beta; TNF, tumor necrosis factor. (Source: Adapted from Marik et al. [487]).

to be associated with LCOS following cardiac surgery in children [457]. The diagnosis of CIRCI in children following congenital heart surgery remains difficult. Studies in this patient population report an incidence of 17–47%, but there is little agreement on the definition of CIRCI and the studies vary widely in the diagnostic criteria used [458–462]. In 2007, Menon et al. found no consensus among pediatric intensivists or endocrinologists as to the incidence or definition of adrenal insufficiency. Pediatric endocrinologists commonly use a cortisol level <18.1 μg/dL following a corticotropin stimulation test, whereas pediatric intensivists made the diagnosis most commonly when a baseline serum cortisol was less than 5 μg/dL. Similarly, there is wide practice variability as to the patients who receive steroids, dosing, and what type of corticosteroid is administered [463].

There is substantial debate as to whether total cortisol (bound and unbound fractions) is an adequate reflection of the activity of the HPA axis when only the unbound fraction is thought to be biologically active. In a study whose purpose was to examine the effect of CPB on the HPA axis in children undergoing cardiac surgery, Wald et al. looked at the correlation of postoperative free and total cortisol levels and CBG levels with clinical outcomes. Interestingly, in their cohort of 51 patients, CBG levels varied widely and decreased from 28.8 ± 9.8 to 22 ± 8.4 mg/L following separation from bypass. Postoperative CBG levels <19 mg/L correlated with increased length of stay and greater inotrope scores, even when adjusted for age and bypass duration. CBG levels were also independent predictors of inotrope score and fluid requirement in the first 24 hours postoperatively using multivariate analysis [464]. Building upon their previous study, Wald et al. measured several markers of endocrine function (total cortisol, free cortisol, ACTH, and CGB) in infants undergoing cardiac surgery who received dexamethasone and the hormonal response to cosyntropin at three different time points: immediately before CPB, at arrival in the ICU, and 24 hours after surgery. There was a significant decline in all aspects of the HPA axis; however, these low values did not correlate with clinical outcomes. However, patients with an inadequate response to cosyntropin (<9 mg/dL) during the postoperative period required increased fluid resuscitation and had longer lengths of stay [464]. In a prospective observational study of adrenal function in children undergoing Norwood palliation or interrupted arch with ventral septal defect (VSD) repair, Mackie et al. found that higher total cortisol levels correlated with lower cardiac index and higher atrial filling pressures at 48 hours postoperatively [459]. Although some postoperative patients have laboratory evidence of suspected CIRCI, there is conflicting evidence of a link to clinical outcomes in the first postoperative days [459–461, 465].

Management of CIRCI

Annane et al. published a trial in which corticosteroid supplementation was found to reduce mortality in adult patients with septic shock [466]. Subsequently, a larger prospective trial of corticosteroid administration in adult septic shock failed to demonstrate the same mortality benefit [467]. Several studies have recently been published examining the effect of steroid supplementation in children following congenital cardiac surgery. A Cochrane review published in 2020 reviewed the available studies to determine the usefulness of prophylactic administration of steroids for children undergoing cardiac surgery. Methylprednisolone, hydrocortisone, and dexamethasone were the steroids investigated. Based on analyses, it was found that corticosteroids do not change the risk of mortality for children undergoing heart surgery utilizing CPB. While corticosteroids were found to reduce the duration of mechanical ventilation, they did not result in shortened length of intensive care or hospital stay [41].

The administration of corticosteroids in the setting of suspected CIRCI in the postoperative period has been associated with improved hemodynamics [457, 468, 469]. Millar et al. reviewed the hemodynamic effects of corticosteroid administration. In those children who had undergone cardiac surgery, 41% demonstrated a greater than 20% increase in mean arterial pressure within 24 hours of steroid administration [470]. A positive hemodynamic response to steroids did not correlate with random total cortisol levels. A summary of the studies to date evaluating the effects of postoperative glucocorticoid administration is summarized in Table 12.6 [471].

Corticosteroid administration is associated with well-known risks. Infection, altered glucose metabolism, difficulty with wound healing, elevation in white blood cell count, and adrenal suppression are among these risks. Certainly, the short-term hemodynamic benefits may outweigh these risks in the most critically ill subset of patients following congenital cardiac surgery. Most of the studies examining the administration of corticosteroids in this patient population reported no increase in hyperglycemia or white blood cell count [457, 458]. There is some evidence to suggest that an increase in mediastinal infection may be seen in those receiving perioperative steroids in low-risk surgical patients or in those with the highest number of days of corticosteroid exposure [472]. In a retrospective review of children less than 5 years of age undergoing cardiac surgery at a single center, cumulative days of corticosteroid exposure were independently associated with risk of infection [429, 472]. Additionally, there is increasing concern regarding the negative long-term cognitive and neuromotor consequences of steroid exposure during the neonatal period [473]. Given the current data, it is important to carefully consider the routine treatment of low total cortisol with exogenous glucocorticoids.

There is no consensus on the use of corticosteroids in pediatric patients undergoing cardiac surgery, and there is a wide variability in practice. More recently, there are several collaborative efforts to perform randomized, double-blind, placebo-controlled multicenter trials. The DECISION trial was performed in four centers (Brazil, China, and Russia) and administer placebo or dexamethasone in children less than 1 year of age undergoing cardiac surgery utilizing CPB. Dexamethasone did not significantly reduce major complications or mortality at 30 days [474, 475]. Currently, the STeroids to REduce Systemic inflammation after infant heart Surgery (STRESS) trial is a multicenter study ongoing in the United States. The study will evaluate patients less than 1 year of age undergoing cardiac surgery with CPB and look at several end points, including operative mortality, death or major complication, hospital length of stay, LCOS, or need for additional steroid administration in the first 72 hours after surgery [476].

Table 12.6 Use of steroid therapy postoperatively in children with congenital heart disease

Study	Design	Patients	Intervention	Outcome	Notes
Shore et al. [468]	Retrospective review	<1 year old 38% patients not postoperative	Compared patients treated with high-dose epinephrine with those who received high-dose epinephrine and hydrocortisone	Significant decrease in epinephrine within 12 hours of hydrocortisone. Hydrocortisone-treated patients required longer duration of inotropic support	
Suominen et al. [457]	Retrospective review	Neonates with LCOS who received hydrocortisone	Hydrocortisone for 5 days	Hydrocortisone significantly increased mean and systemic blood pressure, significant weaning of epinephrine within 24 hours of hydrocortisone	
Ando et al. [458]	Prospective RCT	Neonates undergoing biventricular repair	Placebo vs. hydrocortisone for 72 hours followed by 4-day wean	Hydrocortisone group had improved hemodynamics, less positive fluid balance, less body edema, improved oxygenation, shorter duration of mechanical ventilation	
Millar et al. [470]	Retrospective review of patients who received steroids for hypotension	35% of patients not postoperative	28.4% hydrocortisone, 17.6% dexamethasone, 3.9% methylprednisolone	41% had improvement in blood pressure, all patients with response survived. 20% mortality in nonresponders	27.4% nosocomial infections, no GI bleeding
Robert et al. [469]	Double-blind randomized control trial	Neonates undergoing cardiac surgery with cardiopulmonary bypass	Placebo vs continuous hydrocortisone infusion tapered over 5 days	Prophylactic hydrocortisone infusion reduced low cardiac output syndrome, improved fluid balance and urine output	

Original Source: Data from Green and Koch [471].
GI, gastrointestinal; LCOS, low cardiac output syndrome; RCT, randomized controlled trial.

Stress hyperglycemia

Collectively, hyperglycemia, insulin resistance, and glucose intolerance in the setting of acute illness are referred to as stress hyperglycemia [477]. Studies have shown both a strong correlation between stress hyperglycemia and poor outcomes and a linear relationship between the degree of hyperglycemia and disease severity [478, 479]. Many clinicians and investigators have assumed this relationship is causal and critical care units have embarked upon protocols targeting various levels of glycemic control. However, studies examining strict glycemic control have not shown improved outcomes [480–482].

Several investigators have suggested that stress hyperglycemia is an adaptive response [483]. Stress hyperglycemia and insulin resistance are phylogenetically preserved responses that allow organisms to survive during stress [484, 485]. The HPA axis, sympathoadrenal system, and pro-inflammatory cytokines work collectively to induce hyperglycemia during stress by increasing gluconeogenesis. Glucose transport from the bloodstream to the cellular membrane depends on two mechanisms: a glucose concentration gradient across the interstitial space and a complex regulation among plasma membrane glucose transporters (GLUTs) that facilitate non-insulin-mediated glucose uptake across the lipid cell membrane [486]. In order for glucose to reach cells with reduced blood flow, stress hyperglycemia increases the glucose diffusion gradient and promotes glucose delivery to the cell. During infection, the regulation of GLUTs may play a role in redistributing glucose away from peripheral tissues and toward immune cells and the nervous system [483]. Hyperinsulinemia, severe acute hyperglycemia, and acute fluctuations in glucose concentrations have been implicated in endothelial cell dysfunction through an exaggerated oxidative stress response, which would support more moderate glucose levels versus tight glycemic control (TGC) [477].

Outcome studies in the pediatric population: Hyperglycemia has been associated with perioperative morbidity and mortality in adult patients undergoing cardiac surgery [487–489]. In the pediatric population, retrospective studies linking hyperglycemia and outcome have yielded mixed results [332, 490–494]. To date, three randomized controlled trials in the critically ill pediatric population have been published [495–497]. In 2009, a randomized controlled trial of 700 critically ill pediatric patients, three-quarters of whom were admitted after cardiac surgery, demonstrated that TGC led to a reduction in vasoactive support, infection rate, ICU length of stay, and mortality compared with usual care [450]. Subset analysis of cardiac patients was not done. In the TGC group, investigators targeted glucose levels of 50–80 mg/dL in infants and 70–100 mg/dL in children aged 1–16 years. The prevalence of hypoglycemia was 25% (70 infants, 17 children), with possible symptoms of hypoglycemia noted in only three patients [497].

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In 2012, the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) study published results of 980 patients younger than 36 months of age who underwent CPB. This was a two-center, randomized controlled trial with patients randomized into either a TGC (glucose levels of 80–110 mg/dL) or a standard care group. In order to minimize the risks of hypoglycemia, a subcutaneous sensor was inserted prior to sternal incision in the TGC group. This sensor was wirelessly paired with a continuous glucose monitor that displayed blood glucose levels every 5 minutes and alarmed if a glucose level dropped below manually set limits. Healthcare-associated infection, organ dysfunction, length of stay, and mortality were no different between the groups. The rate of hypoglycemia (<60 mg/dL) was 19% in the TGC group compared with 9% in the standard care group [495].

Macrae et al. conducted a randomized controlled trial involving children admitted to 13 pediatric critical care units in England [496]. Patients between 36 weeks corrected gestational age and 16 years of age were eligible if they had an arterial catheter in place and were on mechanical ventilation and vasoactive drugs with an anticipated duration of treatment of at least 12 hours. A total of 1,369 children were assigned to either the TGC group with targeted glucose levels of 72–126 mg/dL or the conventional treatment group in which glucose levels exceeding 216 mg/dL were treated until they fell below 180 mg/dL. Two-thirds of patients in this study were admitted to the critical care units following cardiac surgery, and these patients underwent subset analysis. The 30-day primary outcome was the number of children alive and free from mechanical ventilation. Secondary outcomes included ICU and hospital length of stay, duration of mechanical ventilation and receipt of vasoactive drugs, need for renal replacement therapy, incidence of bloodstream infection, use of antibiotics for more than 10 days, number of red cell transfusions, Paediatric Logistic Organ Dysfunction (PELOD) score, rate of readmission to the ICU, and costs. TGC was associated with a smaller proportion of patients receiving renal replacement therapy, yet authors did not report the significance of this in the cardiac population. No difference in other outcomes was found between the TGC and the conventional treatment groups in the cardiac population, yet hospital length of stay and costs were significantly lower in the noncardiac population. Hypoglycemia occurred more often in the TGC group, with an incidence of 15.9% in the TGC group vs. 3.7% in the conventional treatment group [496].

The risk of hypoglycemia

Support for TGC in the pediatric cardiac population remains elusive and is probably due to the feared impact of hypoglycemia on the developing brain. Both hyperglycemia and hypoglycemia have been associated with neurologic damage [498, 499]. Although the major oxidative fuel of the brain is glucose, fetal and neonatal brains also have the capacity to oxidize ketone bodies, lactate, and perhaps amino acids [500–503]. With regard to neurocognitive and developmental outcomes, Mesotten et al. performed extensive neurologic testing in the infants and children in the previously described study by Vlasselaers in which there was a prevalence of hypoglycemia of 25% [497]. At 3-year follow-up, these investigators found that TGC was associated with improved motor coordination and cognitive flexibility and that hypoglycemia was not associated with worse neurocognitive outcome [504]. Alternatively, a 1-year follow-up study by the SPECS group did not find a difference between TGC and standard care on neurodevelopmental outcomes. It did, however, raise concern that patients who had recorded moderate (40–49 mg/dL) to severe (<40 mg/dL) hypoglycemia at times during the study may have worse neurodevelopmental outcomes [505].

In conclusion, there are no clear guidelines for glycemic control following pediatric cardiac surgery and CPB. While hyperglycemia in the early postoperative period is universally seen, it is usually limited and can be attenuated by limiting glucose administration in the intraoperative and immediate postoperative periods [506–508]. Perhaps patients who have persistent hyperglycemia or who fail to convalesce as expected are the subset most likely to reveal the appropriate strategy of glycemic management in future studies [492].

Thyroid hormone

Thyroid hormone has a range of direct and indirect effects on the cardiovascular system that is mediated by genomic and nongenomic mechanisms [509–512]. Administration of triiodothyronine (T3) is associated with a decrease in systemic vascular resistance, an increase in the force of ventricular contraction, and more rapid diastolic relaxation [513–515].

Cardiac surgery, both with and without CPB, is associated with depression of thyroid hormone levels in adults and children. In 1978, Zucker et al. first measured low levels of thyroid hormone and low thyroid-stimulating hormone (TSH) in 19 children undergoing CPB, five of whom were on dopamine infusions that had previously been shown to depress TSH levels in healthy volunteers [516]. Bettendorf et al. measured plasma TSH, thyroxine (T4), T3, and thyroglobulin (Tg) in 132 children undergoing heart surgery before and up to 21 days postoperatively [517]. In addition to 85 patients placed on dopamine infusions, betadine solution was used for operative skin preparation and found to cause low thyroid levels in the neonate. Linder et al. found that postoperative levels of TSH were lowest at day 1, while T3 and T4 were at their lowest on day 2. TSH typically increased to levels above those obtained preoperatively at day 5. Patients on dopamine infusions had the most striking changes in thyroid hormone levels. There was also a significant correlation between postoperative urinary iodine excretion and lowest T3 levels. Investigators also noted longer periods of mechanical ventilation and oxygen supplementation as well as higher inotrope use in patients with T3 levels <0.6 nmol/L [518].

Of interest in these studies was the decrease in TSH levels suggesting changes at the hypothalamic–pituitary–thyroid axis. This pattern is also seen in nonthryoidal illness syndrome, once called "sick euthyroid syndrome," a condition often seen in the setting of critical illness. It is unclear whether nonthryoidal illness syndrome is an adaptive response to critical illness that lowers oxygen consumption and catabolic burden or is maladaptive, potentially resulting in LCOS and organ failure. If maladaptive, could T3 infusions improve cardiovascular performance and improve outcomes?

In adults undergoing coronary bypass surgery, parental T3 repletion improves postoperative cardiac index and lowers

the incidence of atrial fibrillation in select patients [519–522]. In pediatric patients undergoing cardiac surgery, three randomized, placebo-controlled trials of T3 supplementation demonstrated the safety of T3 infusions in the perioperative period but were underpowered to detect differences in clinical outcome. Chowdhury et al. found no difference in inotrope scores, day on mechanical ventilation, or postoperative length of stay, although there was a trend in clinical improvement in neonates [523]. Mackie et al. performed a randomized, double-blind, placebo-controlled pilot trial of T3 in neonates undergoing the Norwood procedure or arch repair with VSD closure [524]. Primary endpoints were a composite clinical score composed of time until negative fluid balance, time until sternal closure, and time until first extubation. No differences were seen in the composite score between the treatment and placebo groups. The authors pointed out that the single variable of time until first negative fluid balance was shorter by half a day in the treatment group ($P = 0.27$). Bettendorf et al. did observe an improvement in cardiac index as measured by echocardiography [525]. A 2004 Cochrane review concluded that there was insufficient evidence regarding risk or benefit from T3 supplementation in the pediatric cardiac surgery population [526].

In 2010, results from the Triiodothryonine Supplementation in Infants and Children Undergoing CPB (TRICC) trial were published [527]. This study was a prospective, multicenter, double-blind, randomized, placebo-controlled trial examining T3 repletion versus placebo in children less than 2 years of age undergoing cardiac surgery. No difference was found between the groups in the primary end point of time from aortic cross-clamp removal to extubation. However, subgroup analysis showed a significant interaction between age and treatment effects. In children less than 5 months of age, T3 repletion shortened time to extubation to a median of 55 hours, compared with 98 hours in the placebo group. In children greater than 5 months of age, there was a small but significant delay to extubation in the T3 group (20 hours in the T3 group, 16 hours in the placebo group). The risk of adverse events was similar between the two treatment groups [527].

In 2012, investigators published results of additional analysis from the TRICC trial examining the relationship between postoperative cytokine and T3 levels [528]. Studies in healthy adults had previously shown that infusion of recombinant IL-6 appeared to decrease T3 levels at 24 hours after the infusion [485]. In 1996, a study by Saatvedt and Lindberg demonstrated a significant inverse correlation between postoperative T3 and IL-6 levels in children following CPB [529]. In the TRICC subgroup, investigators found that postoperative cytokine levels were predictive of T3 levels at 6, 12, 24, and 72 hours. These authors suggested that preoperative screening of certain cytokines might help to risk-stratify patients at risk for prolonged intubation and determine which patients might benefit from postoperative T3 supplementation.

A meta-analysis completed by Flores et al. reviewed 9 studies and included 711 pediatric patients. Dosing and administration of T3 varied widely between 0.4 and 5 mg/kg and a single dose to continued hormone replacement during the ICU stay. The group receiving thyroid replacement required less inotropic support; however, there was no difference in duration of mechanical ventilation, ICU stay, hospital length of stay, and mortality between groups [530]. Ultimately, the effects of CPB on thyroid hormone are well known; however, the clinical significance of thyroid replacement remains equivocal.

KEY POINTS: GASTROINTESTINAL, HEPATIC, AND ENDOCRINE CONSEQUENCES OF CARDIAC SURGERY IN CHILDREN

- Hepatic dysfunction is noted in up to 9% of patients, with shock in the postoperative period being the most frequent risk factor.
- CIRCI can be observed after bypass; diagnosis is clinical and by ACTH stimulation test. It is managed using stress dose corticosteroids.
- Hyperglycemia is common after bypass surgery and does not appear to have a major effect on short- or long-term outcomes in the cardiac population.
- Bypass is associated with decreased conversion of T4 to T3, and supplementation of T3 in infants is associated with shorter time to extubation.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

21 Achey MA, Nag UP, Robinson VL, et al. The developing balance of thrombosis and hemorrhage in pediatric surgery: clinical implications of age-related changes in hemostasis. Clin Appl Thromb Hemost 2020; 26:1–12. Another detailed presentation of the cell-based coagulation model, but with practical significance directed toward developmental hemostasis. Specifically, the authors emphasize how children respond to extracorporeal circulation, major surgery, transplant, and other significant physiologic perturbations.

22 Ho KM, Pavey W. Applying the cell-based coagulation model in the management of critical bleeding. Anaesth Intensive Care 2017;45(2):166–76. The authors present a detailed explanation of the cell-based model of coagulation. They make the model highly relevant to our practice by presenting a practical approach to the bleeding patient.

85 Kenet G, Barg AA, Nowak-Gottl U. Hemostasis in the very young. Semin Thromb Hemost 2018;44(7):617–23. The authors provide a detailed explanation of developmental hemostasis and its relevance for clinical management.

98 Williams GD, Bratton SL, Ramamoorthy C. Factors associated with blood loss and blood product transfusions: a multivariate analysis in children after open-heart surgery. Anesth Analg 1999;89(1):57–64. This classic study of risk factors for perioperative bleeding is still relevant today and is worthy of review.

120 Cholette JM, Faraoni D, Goobie SM, et al. Patient blood management in pediatric cardiac surgery: a review. Anesth Analg 2018;127(4):1002–16. A detailed review of the literature on pediatric blood management following cardiac surgery. A critical review of the type and quality of evidence supporting various interventions is presented, and consensus guidelines are critically evaluated. Finally, the authors review the existing trials on restrictive versus liberal transfusion thresholds in pediatric cardiac surgery.

134 Machovec KA, Jooste EH. ediatric transfusion algorithms: coming to a cardiac operating room near you. J Cardiothorac Vasc Anesth 2019;33(7):2017–29. A very practical, detailed review of transfusion algorithms in pediatric cardiac surgery. Attention is paid to

developing an institution-specific algorithm that considers surgical complexity and overall perioperative risk.

140 Faraoni D, Rahe C, Cybulski KA. Use of antifibrinolytics in pediatric cardiac surgery: Where are we now? Paediatr Anaesth 2019;29(5):435–40. A brief but important review of antifibrinolytics in pediatric cardiac surgery, with emphasis on the varying protocols in the literature.

188 Jooste EH, Scholl R, Wu YH, et al. Double-blind, randomized, placebo-controlled trial comparing the effects of antithrombin versus placebo on the coagulation system in infants with low antithrombin undergoing congenital cardiac surgery. J Cardiothorac Vasc Anesth 2019;33(2):396–402. Recent investigations have identified low AT3 as an independent risk factor for transfusion following cardiac surgery, and this prospective trial of recombinant AT3 has reported efficacy specifically for small infants when this deficiency can be identified preoperatively.

208 Weisel JW, Litvinov RI. Red blood cells: the forgotten player in hemostasis and thrombosis. J Thromb Haemost 2019;17(2):271–82. Do red cells participate in coagulation? We probably did not pay much attention to this question in our training, but the answer is probably yes, and we are just beginning to understand this potentially important issue. The authors unpack a very broad range of laboratory and clinical evidence; this article will make you think.

210 Donahue BS. Red cell transfusion and thrombotic risk in children. Pediatrics 2020;145(4):35. Recent evidence is emerging that red cells probably contribute to coagulation activity, and this, along with several other recent studies, reports that red cell transfusion increases thrombosis risk in pediatric surgery.

CHAPTER 13
Vascular Access and Monitoring

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Introduction

Vascular access is an essential part of anesthetic management in children undergoing cardiac surgery. In children with congenital heart disease (CHD), particularly neonates, it may be extremely difficult to obtain secure vascular access, and thorough knowledge of pediatric vascular anatomy, as well as the skills to cannulate the vessels, is mandatory. Traditional techniques of catheter placement rely mainly on anatomic landmarks, can be time-consuming, and often involve serious risks. Higher rates of successful catheter insertion and lower rates of complications can be obtained with recently introduced ultrasound-guided techniques if properly applied during catheterization. Some complications can be life-threatening, and therefore, many institutions around the world recommend, and sometimes mandate, the use of ultrasound guidance to enhance patient safety, especially in cases of central venous catheter (CVC) placement. Positive outcomes and maximum benefits can only be gained if meticulous attention is paid to every aspect of catheter placement and maintenance. Hence, risk–benefit assessments should always be performed and indications considered. Large-bore peripheral venous catheters are required to administer fluids and blood products with minimal resistance to flow, arterial catheters are used for continuous blood pressure monitoring and blood sampling, and central catheters for direct infusion of vasoactive drugs and bolus administration of resuscitative drugs. Hemodynamic assessment via invasive monitoring is also crucial for understanding and responding in a timely manner to the pathophysiologic processes associated with patients' underlying cardiac conditions and associated surgical procedures. This chapter describes techniques of vascular access for children with CHD, emphasizing ultrasound guidance for successful placement of venous and arterial catheters, and reviews the interpretation of data obtained from invasive monitoring and strategies for avoiding complications.

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Venous access

Peripheral venous access

Peripheral venous cannulation in pediatric cardiac patients can usually be accomplished with few complications. Ideally, a large cannula is inserted into a large vein of the arm or leg, but if this is anticipated as initially difficult, another practical approach can be adopted. A small superficial vein at any site is cannulated with a small catheter (24 or 22 gauge [ga]) before induction or during inhalation induction of anesthesia. Once the airway is secured and the patient immobile, larger-bore venous access can be attempted. Cannula sizes appropriate for intraoperative use are selected according to the patient's weight as follows: <3 kg, 24 ga; 3–10 kg, 22 ga; 11–20 kg, 20 ga; 21–30 kg, 18 ga; >30 kg, 16 ga. Typical locations for peripheral venous access include tributaries of the cephalic and basilic veins and dorsal metacarpal veins at the dorsum of the hands; basilic, cephalic, and median cubital veins of the forearm; the great saphenous vein at the ankle; the dorsal venous arch of the foot; and the lateral malleolus vein of the lower extremities.

Once the patient is cannulated and in the surgical position, it is important to make sure that each intravenous (IV) line is functioning without abnormal flow resistance before draping is commenced. If flow of the infused fluid in the line is in some way affected by body position (e.g. wrist flexion or extension), cautious monitoring of the catheter during surgery is necessary to avoid extravasation. Only a large-bore, short catheter in a large vein with flow unaffected by positional change should be used for rapid infusion of more viscous colloids or packed red blood cells [1]. Extravasation of these fluids can lead to compartment syndrome and the need for fasciotomy and permanent loss of limb function in severe cases.

Commonly selected locations for this purpose include the saphenous vein at the ankle, the cephalic or basilic vein of the forearm, and the external jugular vein (EJV). When the vein can be successfully punctured but advancement of the catheter to its full length is impossible, a spring-wire guidewire 0.018″ (for 22 ga) or 0.015″ in size may be used to facilitate cannulation [2].

Peripheral vein cannulation in pediatric patients is not always an easy task; therefore, sufficient planning and preparation often help to overcome anticipated difficulties. One of the useful tools for prediction is the difficult intravenous access (DIVA) score, which consists of four variables to which numbered scores are assigned: three points are given for prematurity; three for age less than 1 year and one point for age 1–2 years; two points for vein not palpable; and two for vein not visible. One study has shown that the first attempt at IV line placement is unsuccessful in more than 50% of children with a DIVA score of 4 or more [3]. The DIVA score has been refined and validated, and three predictors, including history of stay in the newborn intensive care unit (ICU), operator's inexperience, and skin color, have been incorporated [4]. Recognition of a child with a high DIVA score should warn anesthesiologists and prompt them to prepare a backup plan for anticipated difficult peripheral venous access. In the face of unanticipated DIVA, calling for the help of an experienced and skilled anesthesiologist, if available, is far more important than multiple attempts and hope for successful cannulation. Each consecutive puncture and failed cannulation increase difficulty of subsequent attempts and risk of complications.

New technologies have been developed in the past several years to facilitate venous access in children, with variable results [5–9]. Among them, ultrasound and illumination techniques are promising, particularly in children with anticipated cannulation difficulties. Ultrasound-guided methods for peripheral IV access will be discussed in detail later in this chapter. With respect to illumination techniques, a few commercially available vein locator devices can be used. The AccuVein® AV300 or AV400 (AccuVein Inc., Huntington, NY, USA) is a vein illumination device that operates by projecting infrared light, which is absorbed by hemoglobin, and making the veins visible through a viewfinder. The VeinViewer® (Luminetx Corp., Memphis, TN, USA) uses near-infrared light and projects a real-time image of the vein pattern directly onto the patient's skin. Neither obesity [5] nor skin color [6] interferes with vein visibility. Although the efficacy and use of these devices under routine and anticipated difficult IV access conditions have not been validated in large-scale studies of pediatric patients, further evaluation would be beneficial because they are easy to operate, non-invasive, and portable.

Technique. Venipuncture is simple and common for all peripheral veins. For veins of the dorsum of the hand, holding the hand in place with the wrist fully flexed while stretching the dorsum of the hand with one's thumb and index finger makes the dorsal metacarpal veins easier to cannulate (Figure 13.1A). If the vein is visible or palpated, the puncture is straightforward. If the vein is not visible or cannot be palpated, blind insertion attempts have traditionally been made based on typical anatomic locations. However, new devices, such as the VeinViewer, may visualize the vessel and facilitate successful cannulation (Figure 13.1B, C). Even if blood flow is not observed in the cannula, it may be advanced into the vessel and cannulation can be confirmed by an infusion trial with a small amount of infusate. Lack of signs of local extravasation indicates successful cannulation.

Central venous access

Central venous access is often necessary during surgery for congenital heart defects to measure central venous pressure (CVP), deliver vasoactive drugs or high-osmolarity solutions into the central circulation, and to repeatedly sample blood to monitor venous oxygen saturation and other metabolic parameters. To achieve these goals, multi-lumen catheters are recommended. The largest distal lumen should be used for pressure monitoring, whereas proximal lumen(s) should be used for other purposes including administration of vasoactive medications. Because large-size catheters in small vessels are associated with higher rates of thrombosis, the size of the catheter should be the smallest acceptable.

In patients with single-ventricle physiology who have undergone palliative cavopulmonary anastomosis surgery, a catheter inserted via the upper limb or neck veins [10] can be used to measure pulmonary artery pressure, which may be important to assess. If access is required only for inotrope infusion, it would be prudent to insert the line elsewhere because thrombosis or occlusion of the superior vena cava (SVC) would limit pulmonary blood flow [11, 12]. Catheters inserted from below the diaphragm should reach the inferior vena cava (IVC) for accurate assessment of atrial pressure [13]. In patients



Figure 13.1 Peripheral venous access with the VeinViewer. (A) The VeinViewer could not show the left dorsal metacarpal vein in a patient aged 9 months. (B, C) The VeinViewer clearly showed the left dorsal metacarpal vein in another patient aged 2 months.

with single-ventricle physiology and adequate atrial septectomy, monitored pressure reflects systemic ventricular diastolic pressure. If complete atrial or ventricular mixing is observed, line flushing or bolus administration of drugs should be performed with care, because clots or inadvertent air infusion can result in paradoxical systemic embolism.

Percutaneous central venous access

Among various available approaches to central venous access, the percutaneous approach has become standard practice at many institutions. This has been particularly true because of the development and widespread use of portable ultrasound devices for ultrasound-guided catheter insertion (see later). Common sites for percutaneous central venous access include the internal jugular, subclavian, and femoral veins. Various central catheters are commercially available. Recommended sizes and lengths for each insertion site are listed in Table 13.1.

Full barrier precautions are mandatory upon catheter placement. Sterile technique with gowns and wide draping should be applied during all percutaneous central cannulations to reduce the risk of catheter-associated infection. After sterile skin preparation with chlorhexidine-containing solution or iodine, wide draping is performed, preferably with a clear, fluid-impermeable, adhesive and aperture drape so that the underlying anatomy is clearly visible. The Seldinger technique is the standard approach. The basic principle is to place a guidewire into the target vessel and then thread a large-bore catheter over the guidewire. For guidewire placement, either an introducer needle or an angiocatheter (catheter-over-needle) may be used. The authors' preference is to use an angiocatheter in infants weighing less than 10 kg (see Figure 13.2). In these patients, a 4 Fr central catheter is routinely used. A 0.015″ or 0.018″ guidewire should be used for cannulation. The wire is first threaded into a 24 ga catheter to enter the vessel. Using this small, 24 ga angiocatheter to puncture the vessel may minimize hematoma formation should inadvertent artery puncture occur, and reduce damage of the vessel should the needle penetrate its posterior wall. Once the catheter is placed in the vein, a short extension tube can be attached and used as a manometer to verify venous access. This verification is extremely important in patients with cyanotic lesions, because the color of blood aspirated from the catheter is not a reliable indicator of correct venous placement. One advantage of an introducer needle is that threading the outer catheter over the inner needle is not necessary. Disadvantages include the necessity to use a large needle (20 ga for a 0.018″ or 0.021″ guidewire) and the possibility of damaging the guidewire if improperly inserted, which can lead to serious complications. Because the tip of the needle may damage the structure of the thin guidewire, attention should be paid not to retract the guidewire through the needle while it is still in the vessel if there is any resistance at all; they should be removed simultaneously to avoid breaking the guidewire and a fragment being retained intravascularly. Guidewires with straight, slightly curved (angled), or J-shaped tips are available. The shape of the tip may be one of the causes of unsuccessful threading [14], particularly in neonates or small infants. The radius of the curvature of the wire's J-shaped tip is often identical to or larger than the diameter of the infant's vessel (~5 mm) [15, 16]. Our preference is to use the straight end of the guidewire in this patient population (see Figure 13.2). After the desired vein is punctured, the guidewire is carefully advanced into

Table 13.1 Recommended central venous catheter sizes and lengths

Patient height (cm)	Internal jugular/ subclavian vein	Femoral vein
<60	20 ga, single lumen, 8 cm 3–4 Fr, double lumen, 8 cm	20 ga, single lumen, 12 cm 3–4 Fr, double lumen 12 cm
60–80	4 Fr, double lumen, 8 cm	4 Fr, double lumen, 12 cm
80–130	4 Fr, double lumen, 12 cm	4 Fr, double lumen, 12–15 cm
130–160	5 Fr, double lumen, 12–15 cm	5 Fr, double lumen, 15 cm
160–170	7 Fr, double lumen, 15 cm	7 Fr, double lumen, 20 cm
>170	8 Fr, double lumen, 16 cm	8 Fr, double lumen 20 cm

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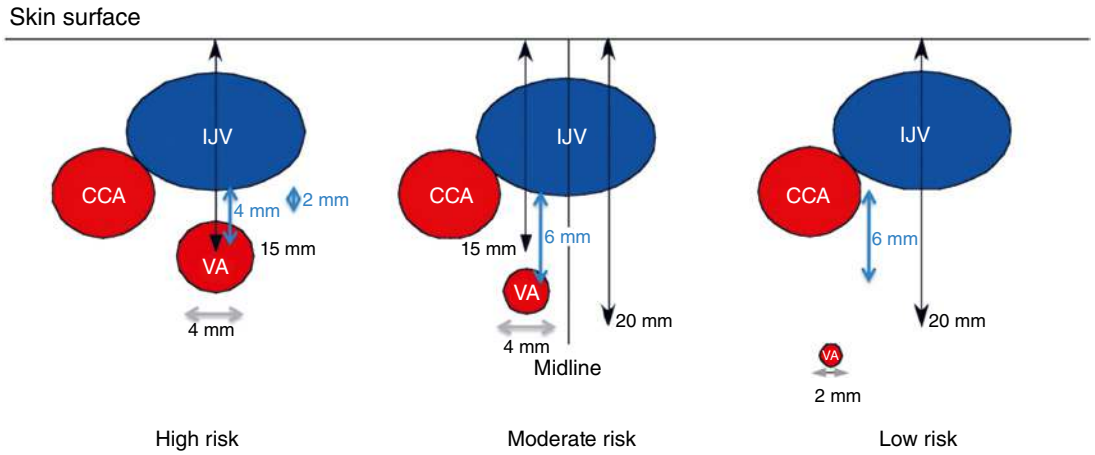


Figure 13.2 Schematic representation of risk classification for vertebral artery puncture. The width, depth from the skin, the distance from the IJV of the VA, and the overlapping between the IJV and VA are illustrated using out-of-plane Doppler color flow imaging. In high-risk cases, the vertebral artery (VA) is wide (>4 mm), locates shallow (<15 mm from the skin), near the internal jugular vein (IJV) (<2 mm), and overlaps with the IJV. In low-risk cases, the VA is small (<2 mm), locates deep (>20 mm from the skin), distant from the IJV (>6 mm), and does not overlap with the IJV. The common carotid artery (CCA) does not affect the classification.

the SVC. The resistance to the wire's passage should be minimal; if any resistance is encountered, the wire must be carefully withdrawn. Forcing a guidewire in the presence of resistance can lead to significant complications. The electrocardiogram (ECG) should be observed carefully as the guidewire is slowly advanced. Premature atrial contractions (PACs) are usually observed as the first guidewire-induced dysrhythmias, signifying atrial location. If no PACs occur, the guidewire is most likely not in the atrium. Premature ventricular contractions, especially if multifocal in nature and occurring as the first observed dysrhythmia, indicate that the guidewire is probably in the ventricle and should be immediately withdrawn. Insertion of a transesophageal echocardiography (TEE) probe before attempting central venous access may facilitate visualization of the guidewire and confirmation of its correct location [17].

After guidewire placement, a very small incision is made followed by careful dilation and catheter cannulation. Dilators included in prepackaged CVC kits are often one size larger than the catheters (e.g. a 5 Fr dilator for a 4 Fr catheter). This might not be optimal with small infants; passage of the catheter without dilation or use of a dilator of the same size as the catheter would be preferable. This allows for the smallest possible entry into the vein, to minimize bleeding and trauma to the vessel wall, both of which can lead to thrombosis or vascular insufficiency. In small infants, attention should be paid to blood loss during the catheterization procedure; direct compression of bleeding puncture sites with the heel of the non-dominant hand should be applied while threading dilators or catheters. Difficult catheterization often requires more hands, and assistance should be requested accordingly. Once the catheter is advanced to the desired depth, it should be secured with sutures and dressing.

Internal jugular vein

The internal jugular vein (IJV) originates from the jugular foramen at the base of the skull. The right IJV is large and lateral to the common carotid artery (CCA) along most of its length (termed the carotid sheath) and is the most common site for central venous access in pediatric patients undergoing cardiac surgery. The IJV provides a direct route to the right atrium (RA) and is an optimal site for catheterization. In patients with supracardiac-type total anomalous pulmonary venous return (TAPVR), the vertical vein draining blood from the common chamber to the brachiocephalic vein and the left IJV and left subclavian vein (SCV) usually contains oxygen-rich blood. Oxygen-rich blood can be drawn while puncturing the left IJV, and it is sometimes difficult to distinguish whether the blood is from an artery or a vein. We recommend use of a pressure transducer for confirmation. Some surgeons discourage the use of the left veins in TAPVR. The right IJV, right SCV, or femoral veins (FVs) can be used instead of the left IJV and/or SCV.

Some simulated models have shown that penetration of the posterior wall of the IJV is unavoidable [18, 19]. Inadvertent CCA puncture can occur unless its exact location is known. The CCA and IJV overlap area differs among studies from various countries and approaches [20–23]. Both the lower approach (at the junction of the two heads of the sternocleidomastoid muscle) and the higher approach (at the cricoid cartilage) provide a similar pattern of overlap (Table 13.2). The overlap between the IJV and the CCA increases with head rotation to either side [24]. In addition, the right IJV is preferred to the left because of a smaller overlap area with the CCA on the right side and its more lateral position [24]. Greater head rotation (more than 30°) to the left should be avoided, because this increases the right IJV and CCA overlap and risk of carotid puncture. Positive inspiratory pressure, but not the Trendelenburg position, can increase the cross-sectional area of the IJV [25]. Use of combination of the Trendelenburg position, liver compression, and simulated Valsalva maneuver can effectively increase the diameter of the IJV [26]. Gentle skin traction can also improve the success rate of catheterization [27]. An anchoring maneuver using a pilot needle facilitates IJV catheterization at its

Table 13.2 The overlapping of the right common carotid artery (CCA) and internal jugular vein (IJV) in pediatric patients

	CCA IJV	IJV CCA	IJV CCA
Higher approach (n = 130)	43.1%	43.8%	13.1%
Lower approach (n = 216)	35.2%	53.2%	11.6%

The CCA and IJV are at the cricoid cartilage in the higher approach and at the junction of the two heads of the sternocleidomastoid muscle in the lower approach. Schematic representation of CCA and IJV as imaged by ultrasound with operator standing at patient's head. Results are combined from studies [19–22].

entry in the majority of infants. If the pilot needle is left in the IJV, and the IV catheter (22 or 24 ga) is passed just posterior to the puncture point of the pilot needle to track the pilot needle path at a 10–20° angle to the skin, a natural tumbling movement of the pilot needle helps to anchor the anterior wall of the IJV and facilitate puncture with the catheter needle [28]. The bevel-down approach to the right IJV may decrease the incidence of posterior venous wall damage and hematoma formation compared with the bevel-up approach [29].

Technique. With a landmark approach, the location of the clavicle, sternocleidomastoid muscle, and cricoid cartilage should be confirmed by visually observing and palpating the neck. After disinfecting the insertion site, the skin is usually punctured midway between the mastoid process and the sternal notch in the "high" approach, at the junction of the two heads of the sternocleidomastoid muscle or at the level of the cricoid cartilage in the "middle" approach, or near the jugular notch in the "low" approach (Figure 13.3). After aspiration of dark-colored blood from the punctured vessel, the Seldinger technique should be used for guidewire and catheter placement (described earlier). If the artery is inadvertently punctured, compress the puncture site for several minutes to ensure hemostasis. Ultrasound-guided puncture will be discussed in detail later in the chapter.

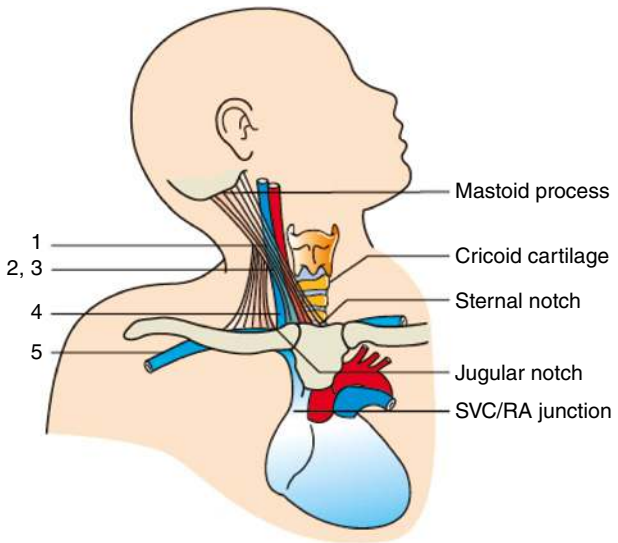


Figure 13.3 Sites for central venous cannulation of the superior vena cava (SVC). 1, high approach, midway between mastoid process and sternal notch; 2, 3, middle approach using apex of muscular triangle or cricoid cartilage; 4, low approach using jugular notch; 5, lateral approach to subclavian venipuncture. RA, right atrium. (Source: Andropoulos et al. [30]. Reproduced with permission from Wolters Kluwer Health, Inc.)

Subclavian vein

Subclavian central venous catheterization is a relatively safe procedure, with minimal complications in pediatric patients [31–35]. The SCV is an extension of the axillary vein at the outer border of the first rib, lies under the clavicle, and runs in the subclavian groove on the first rib. The SCV joins the IJV to form the brachiocephalic vein. It lies anterior to the anterior scalene muscle, and the subclavian artery lies posterior to the anterior scalene muscle. Catheterization of the SCV has several advantages, including its relatively constant position in reference to surface landmarks in patients of all ages, comfort for the awake patient, and less tip migration and greater stability with patient movement. Disadvantages include risk of pneumothorax and the potential inability to dilate the space between the clavicle and the first rib. There is also a possibility that a subclavian catheter will enter the contralateral brachiocephalic vein or ipsilateral IJV instead of the SVC.

Technique. For right-side subclavian venous puncture, positioning with the patient's right upper arm abducted 0° maximizes clavicle and SCV overlap. In the 5°–10° head-down tilt position, puncture the skin near the clavicle at the midpoint or just lateral to the clavicle. Advance the tip of the needle to contact the clavicle. The tip should then be advanced underneath the clavicle with the needle kept in the horizontal position to avoid puncturing the subclavian artery or the lung. When no blood return is obtained, withdraw the needle gently while pulling back the plug with the syringe attached to the angiocatheter. After obtaining dark-colored blood return without pulsation, cautiously advance the guidewire and then the dilator.

External jugular vein (EJV)

The course of the EJV can be readily seen on either side of the patient's neck. The EJV can also be used as a peripheral vein that provides rapid and easy vascular access. Inadvertent arte-

rial puncture is extremely rare with this approach. Although the EJV is a viable site for central venous access with a low complication rate, the EJV has positional concerns because of its angle relative to entry to the SCV, which may hinder the passage of a guidewire into the SVC. This is particularly true in younger patients. Success rates of percutaneous central catheterization via the EJV vary from 54 to 90% [36–40].

Technique. With the patient's head extended, the central portion of the EJV compressed, and the EJV stretched peripherally, puncture the skin with an angiocatheter (<10 kg, 22 ga; 10–20 kg, 20 ga; >20 kg, 18 ga) and insert a curve-tipped guidewire after obtaining dark-colored blood. A small incision with a 25–27 ga needle at the insertion point can aid angiocatheter insertion.

Femoral vein

Another major site of access to the central circulation is the FV. The FV is the most commonly accessed central route in pediatric patients outside the operating room (OR) because of the relatively high rate of success and low incidence of complications [41, 42]. Once thought to be associated with an increased risk of infection, studies have since concluded that cannulation of the FV is of no greater risk than other sites [43, 44]. Several studies [13] have reported that mean CVP measured in the IVC below the diaphragm is identical to that measured in the RA in patients with or without CHD (in the absence of increased intra-abdominal pressure or IVC obstruction). Agreement of IVC and RA pressures in patients with an interrupted IVC with azygos vein continuation into the SVC, commonly seen in heterotaxy syndrome, have not been evaluated; however, the catheter can be used for other purposes such as drug or fluid infusion.

Technique. The patient should be positioned with a rolled towel placed under the hips to obtain moderate extension. The puncture site should be 1–2 cm inferior to the inguinal ligament and 0.5–1 cm medial to the femoral artery impulse, with the needle pointed toward the umbilicus. Ultrasound guidance is useful for identifying important anatomic structures to aid in successful, uncomplicated placement (see later). It is important to puncture the vessel below the inguinal ligament to minimize the risk of retroperitoneal bleeding. Once cannulated, the Seldinger technique should be used as for IJV cannulation. The tip of the catheter should be located in the mid-IVC.

Umbilical vein

In neonates, a catheter can be placed in the umbilical vein for emergency access when peripheral venous access is not readily available [45, 46]. This vessel can be cannulated at the umbilical stump up to a week after birth. Therefore, umbilical line placement is often performed by physicians in the neonatal ICU.

At some institutions, umbilical catheters are routinely used in neonates with cardiac disease for whom surgery is planned in the first 2 weeks of life [47]. Catheters (5 Fr double- or triple-lumen umbilical venous catheters) are used to infuse volume and vasoactive drugs as well as to concomitantly monitor CVP. One benefit of using the umbilical vein is that it spares the femoral, jugular, and subclavian veins from the risk of thrombosis and permanent occlusion. This is particularly important in neonates with specific diseases in whom multiple interventions are inevitable as they grow older. One caveat is that if the ductus venosus closes after birth, the umbilical catheter does not pass into the IVC, often ending with the catheter tip in branches of the hepatic vein. If on radiography the tip of the catheter is located at sites other than the IVC, the catheter should not be used as a central line.

Technique. With the sterile technique and after placing a loose tie of vessel tape around the umbilical base, the two thick-walled umbilical arteries and the single thin-walled umbilical vein can be readily identified. While dilating with a hemostat, the catheter can be passed easily without a guidewire. If resistance is minimal, the catheter can be advanced to a premeasured distance (usually 7–12 cm). Catheter tip position should be determined radiographically as early as possible to confirm its passage through the ductus venosus and into the IVC.

Direct transthoracic intracardiac vascular access

Intracardiac catheters are generally inserted by the surgeon under direct visualization into the right or left atrium [48, 49] and secured by a purse-string suture [50]. Pulmonary artery (PA) catheters can be located high in the right ventricular outflow tract through the pulmonary valve, or in the main PA. Continuous monitoring of mixed venous saturation in the PA or SVC with an oximetric catheter can be performed with this procedure [48]. Monitoring of continuous SVC oxygen saturation has been shown to be very useful in the post-bypass management of neonates undergoing the Norwood procedure for hypoplastic left heart syndrome [51]. Intracardiac catheters are usually placed during the rewarming phase on cardiopulmonary bypass (CPB) and may be used for pressure monitoring or administration of vasoactive drugs. The benefits of this approach include less time spent on CVC placement, assurance of the location of the catheter tip, and no potential harm to the vessel. Disadvantages include unavailability of central access in the pre-bypass period and a higher risk of cardiac tamponade after catheter removal. Due to this potential risk of post-removal bleeding, mediastinal drainage tubes are usually left in place until all intracardiac lines are removed. This may also be considered a disadvantage, because removal of the lines may leave the patient without central venous access or may delay discharge from the ICU.

A left atrial catheter is often indicated if ventricular dysfunction, coronary artery perfusion abnormalities, or mitral valve dysfunction is anticipated postoperatively. Pulmonary artery catheters are particularly useful in the management of patients with preoperatively known or postoperatively anticipated pulmonary hypertension (e.g., obstructive TAPVR, complete atrioventricular canal, severe mitral valve disease). A PA catheter may be indicated for infants with pulmonary hypertension and patients with residual right ventricle outflow tract obstruction because pull-back of the catheter can provide a pressure gradient between the right ventricle (RV) and the PA.

Tunneled percutaneous or intracardiac lines

In patients with difficult venous access and an anticipated prolonged postoperative course, a tunneled silicone catheter may be used to ensure long-term central venous access. Hickman and Broviac are brands of single- and double-lumen catheters that provide external access. These catheters can be placed percutaneously in standard fashion as mentioned in the previous section, or placed transthoracically into the SVC or RA, as with a standard transthoracic catheter but with a subcutaneous tunnel separating the skin exit several centimeters from the chest wall entry site. Compared with standard polyurethane transthoracic catheters, these catheters preserve other access sites for possible future interventions and are less thrombogenic.

Ascertainment of correct position of upper body central catheters

Proper placement of CVCs is necessary to prevent complications and to provide accurate CVP measurements. Some experts recommend that the CVC tip should be in the SVC, above the pericardial reflection, to make sure that it is located outside the pericardium. This will minimize the risk of cardiac tamponade should perforation occur. If the CVC tip is located in the more proximal SVC, the risk of thrombosis increases, and the catheter could migrate into other vessels such as the azygos vein, where pressure monitoring will no longer represent CVP. Others recommend that the CVC tip be positioned in the SVC, just above the SVC–RA junction. This will reduce the risk of thrombosis, malposition, and tip perforation and increase the longevity of the catheter. Various methods have been proposed to determine proper placement and will be discussed below. In the OR setting, TEE-guided catheter tip positioning is a reliable and safe method and thus can be considered the gold standard [17].

Echocardiography

Transesophageal echocardiography is used for many congenital heart operations. Catheter tips and guidewires are easily imaged with TEE, and one study using TEE-guided CVC placement demonstrated a 100% success rate for correct placement in the SVC when TEE was used, as compared with 86% when surface anatomical landmarks were used in infants and children undergoing congenital heart surgery [17]. The TEE probe is placed before CVC attempts are made, and the SVC–RA junction in the 90° plane is imaged. When the vessel is punctured and the guidewire passed, it should be visualized passing from the SVC into the RA. Then the catheter is passed to its full length, the guidewire removed, and the tip of the CVC identified. Flushing the CVC with saline creates an easily visible stream of contrast which identifies the tip. The CVC is then pulled back until it is above the RA, in the distal SVC 1–2 cm above the crista terminalis. Using this technique, immediate, accurate confirmation of placement is obtained before final securing, and before the surgery. The proximal SVC, which is more than 2 cm above the RA, is difficult to image using TEE, so this method is most accurate in placing CVC in the distal SVC. Also, the commonly accepted radiographic SVC–RA junction is often higher than the SVC–RA junction noted by TEE [17].

Transthoracic echocardiography can also be utilized for SVC catheter placement. Park et al. reported 106 right IJV catheter placements in 2- to 12-month-old infants undergoing cardiac surgery [52]. TTE was 96.2% successful at identifying the crista terminalis and allowing placement of the CVC tip within 10 mm above this structure. A 4–10 MHz wide band linear echo probe with standard cardiac ultrasound machine was used in transverse plane at the right second, third or fourth intercostal space. Cross-sectional images of the ascending aorta, PA, and SVC were obtained, and then the probe was rotated 90° clockwise to obtain images of the SVC–RA junction. The catheter tip was advanced to the desired location, with saline flush aiding in identifying the tip. Two-thirds of the catheters could be visualized using the longitudinal view; the others could be visualized using the transverse short axis view with the catheter identified as a white dot in the SVC, and placed at the level of the PA bifurcation.

Radiography

The chest radiograph is still considered the gold standard to confirm proper placement of the catheter [53]; however, post-insertion chest radiography before surgical incision merely to confirm placement of the catheter tip may not be justified in the OR in terms of time, cost, and radiation exposure to the patient. A chest radiograph should be routinely obtained immediately after surgery to reconfirm catheter tip location; the catheter tip should be seen in the area from the level of the first rib to above the pericardial reflection. Based on studies on embalmed and fresh cadavers, the carina is an easily recognizable radiographic landmark in pediatric patients and can be used to confirm that the catheter tip is outside the cardiac chamber [54]. The caveat is that the commonly accepted radiographic SVC–RA junction is often higher than that noted by TEE [55]. Therefore, the catheter tip located within the atrial silhouette on the chest radiograph can be outside the atrium as documented by TEE. Furthermore, an SVC catheter directed posteriorly down the azygos vein may not be detected by anteroposterior chest radiography alone.

Electrocardiographically guided placement

Intravascular ECG may be used in children to guide correct CVC placement [56, 57]. A normal or hyperosmolar (3%) saline-filled lumen with a special ECG adaptor or a guidewire within the lumen attached to a sterile alligator clip serves as an exploratory electrocardiographic electrode. Prepackaged CVC sets are commercially available to allow intracardiac ECG monitoring [58]. A sudden increase in P-wave size (P atriale) occurs as the catheter enters the RA. The catheter tip can then be pulled back 1–2 cm to the desired position within the SVC. Because this method requires special equipment not always available in the OR, TEE can be used as a sufficient substitute.

Height- and weight-based formulae

In the absence of TEE guidance or intravascular ECG, CVC tip position may not be confirmed until postoperative chest radiography, allowing for any potential malpositioning to persist undetected. One study proposed formulae to predict

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the depth of CVC insertion, with the aim of preventing inadvertent catheter tip placement in the RA [30]. Using a large database of CVC placement data in children, the following formulas were developed for catheter insertion via the right IJV or SCV, with the targeted location of the catheter tip at the radiographically determined SVC–RA junction:

$$\left[(\text{Height in cm}/10)-1\right]\text{ cm for patients} \le 100\text{ cm in height}$$
$$\left[(\text{Height in cm}/10)-2\right]\text{ cm for patients} > 100\text{ cm in height}$$

The authors also provided a weight-based formula for length of CVC insertion via the right IJV or SCV. Use of these formulae should result in CVC placement in the mid-SVC in more than 95% of patients. Caveats of these simplified formulae are that for the IJV, the puncture site is high, precisely midway between the mastoid process and the sternal notch. For the SCV, the puncture site is 1–2 cm lateral to the clavicle midpoint. The formulae must be adjusted if different puncture sites are desired. In addition, the formulae were developed for targeting of the catheter tip to the radiographic SVC–RA junction. As mentioned earlier, the radiographic SVC–RA junction is usually higher than the TEE-confirmed SVC–RA junction. A more recent study [53] used a smaller number of pediatric patients to provide height-based formulae for determining the depth of the right internal jugular catheter (Table 13.3). They used TEE or intracardiac ECG to precisely guide the catheter tip to slightly above the SVC–RA junction and measured the depth of the CVC at the site of right internal jugular catheterization. The formulas listed here have not been validated for accuracy in a prospective fashion and therefore should be used with caution.

Table 13.3 Recommended lengths for central venous catheter insertion

	Andropoulos et al. [30]	Yoon et al. [53]
Formula	**(Ht/10 – 1) cm if Ht ≤ 100 (Ht/10 – 2) cm if Ht > 100**	**(0.07 × Ht) + 1.7**
Ht (cm)	**IJV/SCV**	**IJV**
40	3.0	4.5
50	4.0	5.2
60	5.0	5.9
70	6.0	6.6
80	7.0	7.3
90	8.0	8.0
100	8.0	8.7
110	9.0	9.4
120	10.0	10.1
130	11.0	10.8
140	12.0	11.5
150	13.0	–
160	14.0	–
170	15.0	–

Ht, height; IJV, internal jugular vein; SCV, subclavian vein.
In two-lumen catheters, the second orifice is usually at 1.5–2 cm from the tip of the catheter. Catheters should be placed more than 4.5–5 cm from the skin. Insertion points differ among patients, especially in the IJV; thus, it is necessary to adjust 0.5–1 cm from the standard lengths.

Peripherally (percutaneously) inserted central catheters

Given its safety and reliability as a method to efficiently obtain central access, the peripherally inserted central catheter (PICC) has emerged as a favorable percutaneously inserted central line in pediatric patients with acute or chronic illness. The PICC line is a thin, soft, and long catheter that can be used for long-term IV antibiotics, nutrition or medications, and blood draws. In use for more than a decade [59], PICCs are routinely used in newborns expected to require prolonged venous access. The complication rate for these catheters is very low [60, 61], and they are generally easy to insert into the central circulation via the antecubital, saphenous, hand, axillary, or wrist veins. Because of the increased popularity of PICCs for IV access in children, many institutions have adopted a team approach for pediatric PICC placement. Most important for successful placement is early access, before the large, visible, superficial veins are exposed to injury from attempts at peripheral IV placement. In critically ill newborns with CHD, it is best to insert a PICC line soon after hospital admission. Commercially available PICCs are 1–5 Fr, single or double lumen, 6–65 cm, and made from polyurethane or silicone. For a newborn, a 2 or 3 Fr PICC line is often used [62]. Centrally delivered medications or fluids are administered through a PICC line; however, these are often inadequate as the sole pre-bypass access for cardiac surgery. Despite the primary intention of PICCs to be placed centrally, only half are successful; however, non-centrally (mid-clavicle and more distal) placed PICCs can still be used safely and reliably for the administration of medications and isotonic fluids. Insertion of PICCs should follow the techniques described for peripheral venous access and central line insertions.

KEY POINTS: VENOUS ACCESS

- Obtaining venous access in infants and children undergoing surgery for CHD can be very challenging. A backup plan should be instituted in the case of anticipated or unanticipated difficult IV access.
- Selection of the catheter size and its insertion site should be tailored to patient characteristics/needs and the nature of the surgical procedure. A strategic approach is necessary to preserve access sites in small infants with single-ventricular physiology.
- For central venous access, the use of full barrier precautions and the Seldinger technique are standard practice.
- Correct position of the CVC tip is important to avoid serious complications. Various methods are available to ascertain proper placement, and understanding the advantages and disadvantages of each method is crucial.

Arterial access

Arterial catheters are necessary during congenital heart surgery to monitor beat-to-beat changes in arterial pressure and to draw intermittent blood samples. Common sites for arterial line

Table 13.4 Recommended catheter sizes and lengths for arterial access based on site and patient weight

Weight	Radial/dorsalis pedis/ posterior tibial arteries	Brachial artery
<2 kg	24 ga	Not recommended
2–5 kg	22 ga	24 ga
5–30 kg	22 ga	22 ga
>30 kg	20 ga	22 ga
Weight	**Femoral/axillary arteries**	
<10 kg	2.5 Fr, 5 cm	
10–50 kg	3 Fr, 8 cm	
>50 kg	4 Fr, 12 cm	

placement include the radial, femoral, brachial, axillary, dorsalis pedis, and posterior tibial arteries. Table 13.4 displays recommended catheter sizes for arterial access based on site and patient weight. Percutaneous entry is often possible, particularly with the aid of ultrasound, but on occasion a cutdown technique may be required to expedite artery access. Ultrasound-guided insertion techniques are discussed later in this chapter. In the study involving brachial, radial, ulnar, umbilical, femoral, and pedal arteries, vascular complications were highest in femoral arterial access in the perioperative setting [63].

Radial artery

This is the most commonly accessible location for initial arterial cannulation in most infants and children. Before cannulation, the Allen's test can be considered to verify sufficient collateral ulnar circulation [64]. Cannulation ipsilateral to an existing or planned systemic-to-PA shunt should be avoided.

Technique. Secure the patient's hand gently to an armboard, with the wrist slightly dorsiflexed and with a small roll underneath it (Figure 13.4). Prepare the skin with antiseptic solution. Use palpation to identify the artery. Alternatively, audio Doppler or ultrasound guidance can be helpful if the pulse is weak. Lighter anesthesia during catheterization may provide a stronger pulse and increase the success rate. Use a 24 or 22 ga angiocatheter flushed with heparinized saline to optimize the flow of blood into the needle hub. The first attempt offers the greatest chance of success; therefore, conditions, such as lighting, positioning, and vessel identification should be optimized. Puncture of the artery is indicated by brisk flashback. Advance the needle and catheter 1–2 mm into the artery to ensure intraluminal placement and attempt to thread the catheter over the needle its full length into the artery. Alternatively, the artery can be transfixed, the needle pulled back, and the cannula gently withdrawn until brisk flashback is observed (Figure 13.4D). The cannula can then be advanced into the artery (Figure 13.4F, G) or a small 0.015″ intravascular guidewire can be inserted into the artery and the cannula advanced over the wire. Either way, minimal resistance signifies successful threading. If the first attempt is unsuccessful, additional attempts can be made at the same site or slightly proximal to it, to avoid areas of arterial spasm, thrombosis, or dissection. Circulation distal to the catheter should be determined by inspection of the color and capillary refilling time of the fingertips and nailbeds and pulse quality as determined by pulse oximetry. We recommend that the catheter be secured with clear adhesive dressing and tape, to ensure that the insertion site and catheter hub are visible.

Femoral artery

The common or superficial femoral artery is large and easily accessible in most patients and is a logical choice when radial arterial access is not available. Our practice is to avoid the femoral artery for prolonged catheterization, when alternative sites are available, because of potential vascular damage of the involved leg. However, if the patient experiences extreme hypotension or peripheral vasoconstriction when no other major vessels are easily palpable, the femoral artery may represent the only viable choice for arterial catheterization. Left-sided femoral artery catheterization is preferred if future cardiac catheterization is anticipated.

Technique. Place a small towel under the patient's hips to extend the leg slightly to a neutral position. Positioning can be aided by slight external rotation with the knees restrained by taping to the bed. After sterile preparation and draping, palpate the course of the superficial femoral artery and puncture the vessel 1–2 cm inferior to the inguinal ligament to avoid puncturing the artery above the pelvic brim, where a retroperitoneal hematoma could form. Audio Doppler or ultrasound can be used to identify the course of the vessel if the pulse is weak. Various puncture techniques are available: direct puncture with an angiocatheter; an introducer needle supplied with a commercially prepackaged kit; or a 21 ga butterfly needle with the extension tube removed. The needles should be flushed with heparinized saline to increase flashback. Use a small, flexible, 0.015″ or 0.018″ guidewire. Threading a polyethylene catheter over the guidewire can often be done without making a skin incision. Importantly, a dilator should not be used because it could cause arterial spasm, dissection, or bleeding if the puncture site is large. Secure the catheter by suturing around the entry site and suturing wings around the hub. Distal perfusion should be assessed immediately, and a pulse oximetry probe should be placed on the foot for continuous monitoring and early warning of poor arterial perfusion.

Brachial artery

The brachial artery has been used successfully as an arterial access site in neonates and small children [65]. However, this site may have theoretical concerns because it has poor collateral circulation compared with the radial, femoral, and axillary arteries, though this has not been proved by any studies to date. The present consensus is that the brachial artery should be reserved for situations when other options are limited, for example, when a right upper-extremity arterial line is necessary to monitor pressure during cross-clamping for repair of coarctation of the aorta, CPB for aortic arch hypoplasia, or interruption.

Technique. A 24 ga catheter should be used in patients weighing less than 5 kg. Restrain the arm in a neutral position on an armboard, and identify the arterial pulse above the elbow crease, above the bifurcation into the radial and ulnar arteries. The method of cannulation is the same as for

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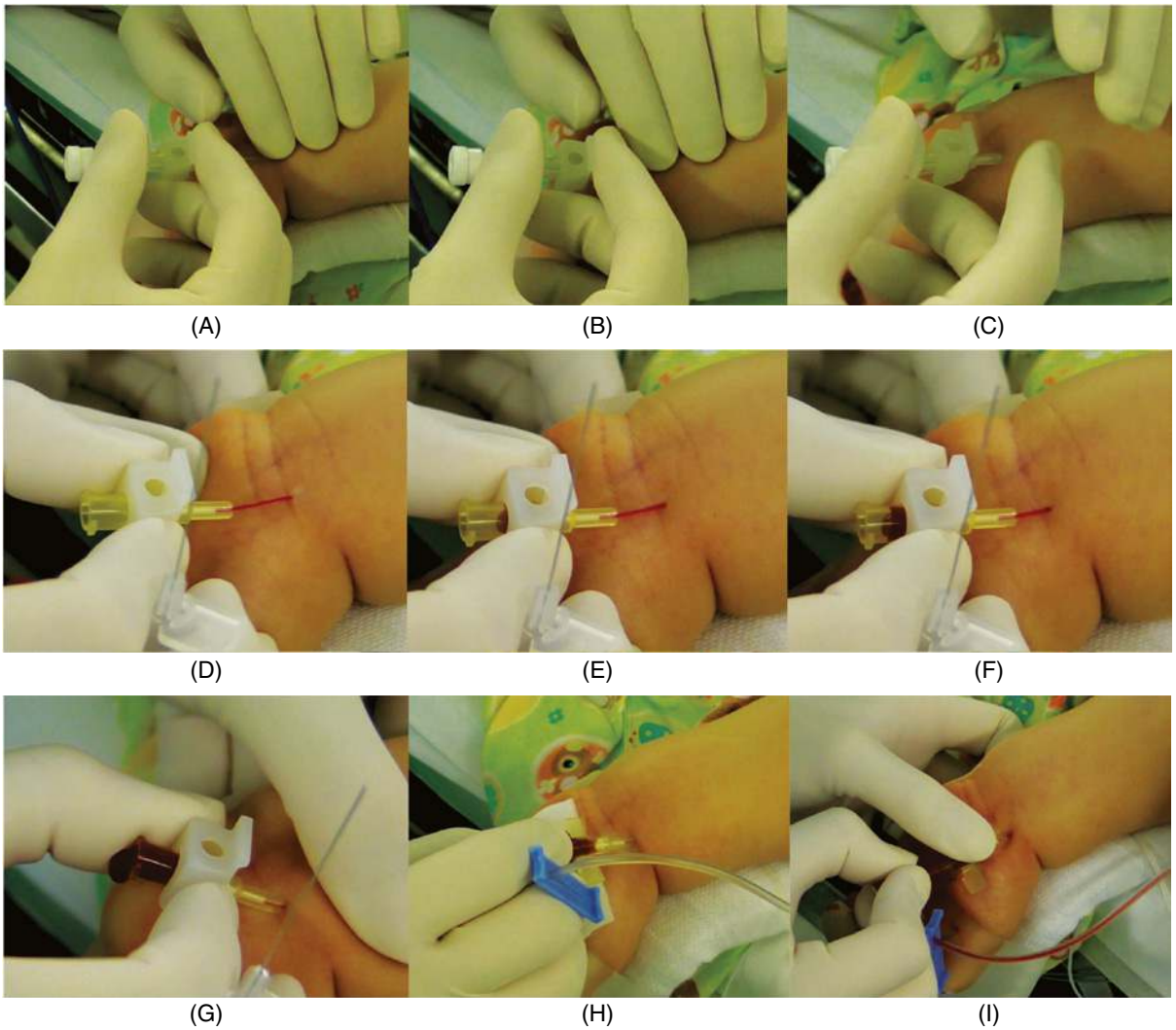


Figure 13.4 Radial artery puncture and catheterization with a 24 ga angiocatheter without ultrasound guidance in a child aged 27 months. The angiocatheter is placed at approximately 10° to the skin (A, B). Blood return cannot be obtained while puncturing (C). When bright-colored blood is obtained from the inner needle of the angiocatheter while withdrawing (D), advance the outer cannula beneath the skin to enter the cannula into the artery (E, F) and confirm continuous blood return (G). A connector is attached to the catheter (H), and arterial blood is aspirated (I).

radial arterial catheterization. Again, distal perfusion should be monitored continuously by pulse oximetry. The catheter should be replaced postoperatively with a catheter at a site that has better collateral circulation as soon as possible.

Axillary artery

The axillary artery is large and well collateralized. Several studies have shown this artery to be a viable option for critically ill children when other sites are not accessible [66–68]. In addition, the complication rate is low. However, given the potential for arm and hand ischemia and intrathoracic bleeding, the axillary artery should be a site of last resort when other options are not available.

Technique. Abduct the arm 90° and extend it slightly at the shoulder. Palpate the artery high in the axilla, puncture with an angiocatheter, and exchange over a guidewire for a longer catheter. A short catheter may be pulled out of the vessel with shoulder extension. Therefore, longer catheters (e.g., 5 cm) are recommended. As with the brachial artery, distal perfusion should be assessed and carefully monitored for potential upper-extremity ischemia. Catheter tip position located outside the first rib should also be confirmed by chest radiography. Because the axillary artery is close to the brachiocephalic artery, it is imperative to flush the catheter gently by hand after blood draws, thereby preventing air bubbles or clots from being introduced into the circulation and minimizing the risk of retrograde cerebral embolization.

Umbilical artery

The umbilical artery can be cannulated in a newborn during the first 72 hours of life and is the site of choice in newborns requiring surgery within a week after birth. Umbilical artery catheterization entails potential risks regardless of the

position of the catheter; placement of the catheter with its tip at the seventh to eighth thoracic segment may be associated with fewer complications than placement at lower positions [69, 70]. Umbilical arterial lines have an uncertain link with necrotizing enterocolitis. A neonate with ductus-dependent circulation, low diastolic pressure, and subsequent systemic steal can be at increased risk of this complication. Umbilical catheters are generally inserted in the delivery room or in the neonatal ICU shortly after birth. Lower-extremity emboli, vascular insufficiency, and renal artery thrombosis have been reported with this site; however, the overall risk is low, and the site is highly desirable because it is a large central artery, which allows for accurate pressure monitoring throughout surgery, while preserving other sites for potential future arterial access.

Technique. Prepare the umbilical stump in a sterile manner and transect. Two small muscular-walled arteries and a larger thin-walled vein are easily identified on the umbilical cord cutoff. Insert a 3.5 Fr catheter blindly into the artery after dilating the vessel. The catheter tip should be placed at the level of the diaphragm or low in the descending aorta, and its position should be confirmed radiographically as soon as possible.

Temporal artery

The superficial temporal artery was widely used, particularly in premature babies. However, it is now avoided because of potentially severe cerebral thromboembolic complications [71, 72]. The exception is when brachiocephalic pressure must be measured during surgery for an aberrant subclavian artery (e.g., corrections for coarctation of the aorta, aortic arch interruption or hypoplasia with an aberrant right subclavian artery arising distal to the obstruction); the only way to measure pressure during cross-clamping or bypass is via direct aortic pressure. This site should be used only during surgery, and the catheter must be removed immediately after operation.

Technique. Use a 24 ga catheter for newborns. Palpate the artery just anterosuperior to the tragus of the ear, just superior to the zygomatic arch. The artery should be approached with a very superficial approach angle (e.g., 10°–15°). Cannulation is performed in the same manner as with the radial artery.

Dorsalis pedis/posterior tibial arteries

Peripheral vasoconstriction and vasomotor instability during the early post-CPB period make the superficial arteries in the lower extremities less suitable as sites for arterial cannulation than the radial artery. An accurate arterial pressure waveform cannot be obtained during the early post-bypass period. These arteries may be indicated for non-bypass surgeries or for continuous pressure monitoring in the ICU.

Technique. For the dorsalis pedis artery, position the foot in slight plantar flexion to straighten the course of the artery, which can be palpated between the second and third metatarsals. For the posterior tibial artery, dorsiflex the foot to expose the artery between the medial malleolus and Achilles tendon. The artery is often deep to the puncture site and may require a steeper puncture angle. Fix the patient's ankle with the arterial line to a board (3) so that the line is not accidentally removed as it is covered by surgical drapes (Figure 13.5).

Ulnar artery

The ulnar artery is only considered when attempts with the radial artery have been unsuccessful or the vessel has thrombosed due to past interventions. It should be used as the last resort, when other options are not available. There is a high risk of ischemia of the hand if both radial and ulnar artery



(A) (B)

Figure 13.5 A posterior tibial arterial catheter. (A) The posterior tibial artery is catheterized with a 24 ga angiocatheter. (B) The patient's ankle with the artery line has been fixed to a board to prevent movement when the line is covered by surgical drapes.

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perfusions are severely compromised. However, one study of 18 ulnar artery catheters in a pediatric ICU reported an ischemia rate of 5.6%, no different from those associated with radial and femoral artery catheters [73].

Arterial cutdown

Cutdown of the radial artery is a reliable and efficient method for establishing arterial access during congenital heart surgery. This method is used as the first and primary method of securing arterial access in some institutions, whereas others only resort to it when all other attempts fail. Despite the speed and ease of access for cutdown, the existing literature indicates that a percutaneous approach is favorable to cutdown in terms of complications (e.g., bleeding, infection, failure, distal ischemia, long-term vessel occlusion).

Technique. Position the arm as for percutaneous radial catheterization. After preparation and draping for surgery, make an incision at the proximal wrist crease, between the styloid process and the flexor carpi radialis tendon. Isolate the exposed artery with a heavy silk suture, vessel loop, or right-angle forceps. It is no longer considered necessary to ligate the artery distally to prevent bleeding; the artery can remain patent after cutdown if not distally ligated. The simplest technique is to directly cannulate the exposed artery with an angiocatheter, in the same manner as for placement of a percutaneous radial artery catheter. Suture the catheter to the skin at its hub and close the incision with nylon sutures on either side of the catheter. To remove, cut the suture at the hub of the catheter, remove the catheter, and apply pressure for a few minutes until bleeding stops. The remaining skin sutures can be removed later.

KEY POINTS: ARTERIAL ACCESS

- In most cases of congenital heart surgery, the radial artery is the preferred site for arterial pressure monitoring, with the second choice being the femoral artery.
- Like venous access, a strategic approach is necessary for selecting the site of arterial access for univentricular patients.
- With a few exceptions, temporal artery cannulation should be avoided because of the risk of devastating cerebroembolic complications.
- Despite theoretical concerns, brachial artery cannulation has been successfully performed in neonates and infants and may be a candidate cannulation site after failure of radial artery catheterization.

Ultrasound guidance for vascular access in congenital heart surgery

Ultrasound-guided vascular access can increase the success rate of line insertion and decrease complication rates associated with catheterization. Ultrasound guidance has been used in many institutions to enhance patient safety, especially during central venous line placement. Understanding the anatomic relations of tissues on sonographically obtained images is essential for safe catheter placement. Fundamental knowledge of the physical principles of ultrasound waves and equipment is necessary for understanding the sonoanatomy of the visualized tissues. Various studies have reported increased success rates and safety of vascular access with the ultrasound guidance.

Sonoanatomy

The differentiation of veins from arteries or muscle can be accomplished with ultrasonography, and it also allows detection of peripheral veins in children. Muscles are moderately echogenic, and adipose tissue is relatively hyperechoic compared with the inner side of a vein filled with low blood echogenicity. Veins are easily compressed, and their lumens are not visible when under compression; thus, they are usually distinguished from muscle or adipose tissue by visual contrast of echogenicity. Another method is to use a low-velocity color Doppler signal (5–20 cm/s), which can be observed as intraluminal color flow. All three layers of a vein wall cannot be distinguished on ultrasonographic images. When the vein is in spasm, the inner layer of the smooth muscle becomes thicker and more visible.

For pediatric vascular access, a linear probe with 5–15 MHz frequency and 1–5 cm depth settings is ideal and adequate in most cases. Higher-frequency ultrasound with 50 MHz can visualize more superficial structures [74]. Various types of portable linear probes are commercially available. Portable ultrasound machines equipped with linear probes are more favorable for pediatric central vein access than larger multifunctional ultrasound imaging systems equipped with TEE probes due to limited space in the OR. A hockey stick-type, 30-mm-wide, small probe might be optimal for vessel imaging, especially in neonates and infants; however, it is sometimes difficult to hold such small probes stably on the tiny necks of neonates and infants. The beveled needle tip produces two echoes, which are obtained when the needle tip reaches the vessel lumen [75]. The distal echo is more intense than the proximal one. The echogenic polymer-coated needle is better visualized than Teflon-coated, etched-tip, echogenic polymer-coated, or untreated needles [76]. Ultrasound also facilitates venous puncture of the great saphenous vein. Direct visualization via ultrasound is a promising technique for the establishment of venous access of the great saphenous vein at the level of the medial malleolus in infants [77].

Ultrasound-guided peripheral vein access

Ultrasound guidance can improve the success rate of peripheral venous access in children with difficult venous access compared with the blind technique [78] and is a promising method. Ultrasound-assisted catheterization saves time spent in the OR when a difficult access scenario is encountered and can, in fact, circumvent this very scenario when chosen as a primary method after adequate patient evaluation. Common veins used include cephalic, basilic, saphenous and brachial veins. The basilic vein is suitable for ultrasound guided peripheral venous puncture because it runs on the convex portion of the foream, making it easy to visualize, especially in lean patients.



Figure 13.6 Positioning of the ultrasound probe for cannulation of the cephalic vein.

Technique. Once a vein has been chosen, search for a long straight portion. During an ultrasound guided approach, it is important to scan the length of the vessel to determine patency and trajectory. The most common technique used is the short axis or out-of-plane approach. The long axis or in-plane approach is preferred by more experienced practitioners, as it allows for dynamic visualization of the needle tip. For the short-axis, out-of-plane technique, place the ultrasound probe at an angle of 60°–80° angle to the skin (Figure 13.6). Sweep or swing the probe along the arm and place it perpendicular to the vein. The vein should be kept continuously in the middle of the visualized field without moving the probe to the side in the perpendicular position. Puncture the skin and visualize the tip of the needle at the center of the anterior wall of the vein. The probe can be moved along the vein while maintaining the probe position perpendicular to the vein. Penetrate the anterior wall with the inner needle of the angiocatheter at an angle of 5°–10° to the skin. Carefully advance the needle, paying attention not to penetrate the posterior wall of the vein. Two high-echoic enhancements from the needle tip placed inside the vessel are observed in the out-of-plane image (Figure 13.7). After obtaining venous blood return from the inner needle, an approximate 2 mm advancement of a 24 ga angiocatheter is required to penetrate the anterior wall by the outer catheter of the angiocatheter. Penetration of the inner needle and outer catheter beyond the anterior wall of the vein is more visible in plane than out of plane. Blood pressure cuff inflation can increase the lumen of the vein in adults and potentially in children.

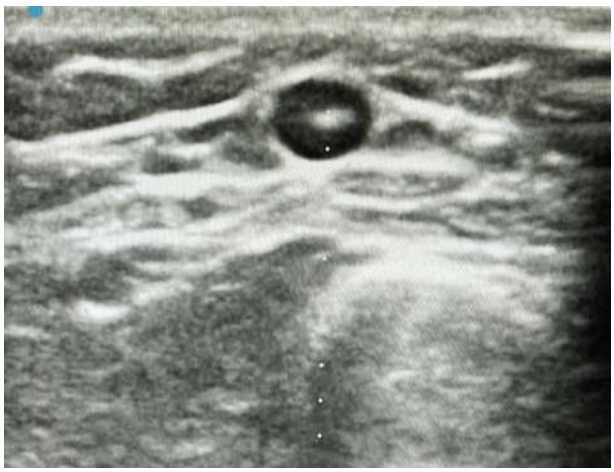


Figure 13.7 Out-of-plane ultrasound image of the cephalic vein with the needle tip as the high echoic signal within the vessel.

After placement of a peripheral venous catheter, if there is a question about whether the catheter is properly sited within the vein, blood return may be elicted with gentle aspiration with larger catheters, and rapid flush of 3–5 mL of saline should be performed. The ultrasound probe can be utilized, especially in small children and infants, to obtain a subxiphoid four chamber view of the heart while saline is rapidly injected into the peripheral catheter. The appearance of saline contrast in the right atrium is confirmation of intravascular placement.

Ultrasound-guided central vascular access

Ultrasound-guided central vascular access has become routine in many institutions, although superiority of either the real-time ultrasound-guided approach or the anatomic landmark approach for locating the IJV has been a matter of debate. The use of ultrasound guidance has been questioned for central catheterization in children; however, many researchers support its application [79–82]. Ultrasound is particularly useful for assisting access to the IJV and FVs in all age groups and the SCV in infants. Randomized studies [80, 83–88] have shown that arterial puncture rates during central catheterization are higher with landmark than with ultrasound guidance (Table 13.5). The use of real-time ultrasound increases insertion success, has higher overall success, reduces access time, and reduces arterial puncture; however, ultrasound-assisted central vein catheterization is not totally reliable. A video analysis reported accidental artery catheterization in five CCAs and one femoral artery despite the use of real-time ultrasonographic guidance, probably due to penetration of the posterior wall of the IJV [89]. Simulated models have indicated that penetration of the posterior wall of the IJV is unavoidable in certain cases [18, 19]. The available evidence tends to support the use of two-dimensional ultrasound to augment the landmark technique for pediatric catheter placement, but more studies are needed [81, 87, 88, 90]. The use of ultrasound during central catheter placement in adults and children remains limited, not universally adhered to, and is

Table 13.5 Arterial puncture rates for ultrasound guidance vs. landmark method during pediatric central venous catheter placement

Author	Arterial puncture (*n*)/attempts (*n*)	
	Ultrasound	Landmark
Verghese et al. [83]	0/43	13/52
Grebenik et al. [84]	7/59	4/65
Arai et al. [85]	0/39	1/42
Leyvi et al. [86]	2/47	3/102
Chuan et al. [80]	1/32	8/30
Froehlich et al. [87]	10/119	18/93
Bruzoni et al. [88]	3/66	7/84
Total	23/405 (5.7%)	54/468 (11.5%)

The inadvertent arterial puncture rate is lower with ultrasound guidance than with the landmark method ($P = 0.0026$).

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most strongly associated with the availability of equipment. Trained anesthesiologists can insert IJV lines safely using the landmark technique [90], and ultrasound-guided insertion techniques require education, training, and practice even when working with the adult patient population. Despite the widespread use of ultrasound in children, formal training for this technique is typically lacking. Trainees may benefit more than experienced operators from the use of ultrasound for central catheterization [91, 92].

Ultrasound-guided IJV puncture

The IJV is frequently used for ultrasound-guided or ultrasound-assisted vascular access in children (Figure 13.8). Ultrasound can be used to place central catheters in the IJV even in neonates and infants. Ultrasonographic localization of the IJV is likely superior to the landmark technique in terms of overall success, speed, and decreased incidence of carotid artery puncture [83]. Both audio Doppler and ultrasound are useful for access to the IJV in children older than 1 year of age [84]. Ultrasound may be more useful than audio Doppler in infants and neonates. Location of the IJV with static ultrasonography and the anatomic landmark approach or combining pre-procedural ultrasonographic assessment with real-time ultrasound-guided venipuncture is recommended for central vein catheterization [79, 93, 94].

In pediatric patients, anatomic structures of the vertebral, thyrocervical trunk, suprascapular, transverse cervical, and inferior thyroid arteries, as well as the CCA, can be observed by ultrasonography including Doppler color flow imaging (Figure 13.8). The brachiocephalic artery divides into the right subclavian artery and the right CCA. The right vertebral artery branches from the subclavian artery. The thyrocervical trunk bifurcates from the subclavian artery next to the vertebral artery and into mainly three arteries, the suprascapular, transverse cervical, and inferior thyroid arteries. Numerous variations have been reported for the vessels arising from the aortic arch [95], with different origin variants of the right vertebral artery and some variants of the thyrocervical trunk and its branches [96]. The vertebral artery usually lies under the CCA and enters the vertebral column at the fifth or sixth vertebra; however, it sometimes lies under the IJV. The relationships between the IJV and the vertebral artery can be seen in out-of-plane images (Figure 13.9A) and in-plane images (Figure 13.9B) with Doppler color flow ultrasound, even in neonates and infants. The depth from the skin to the vertebral arteries, the width of the vertebral arteries, and the distance from the IJVs to the vertebral arteries (Figure 13.2), as well as the extent of overlap between the IJVs and vertebral arteries, with scores of zero to three for each measurement, should be checked [97]. The summed scores are categorized as low risk (0–3), moderate risk (4–7), or high risk (8–10). High risk is approximately 13% for accidental puncture of the vertebral arteries. From the thyrocervical trunk (Figure 13.10A), the suprascapular, transverse cervical (Figure 13.10B), and inferior thyroid arteries arise, in that order. Inexperienced practitioners can mistake these arteries for the vertebral artery with ultrasound imaging of this vessel [98]. In some cases, such as anomalous origin of the vertebral artery or IJV spasm, the relationship between the vertebral artery and the IJV may be more clearly understood with in-plane imaging [99].

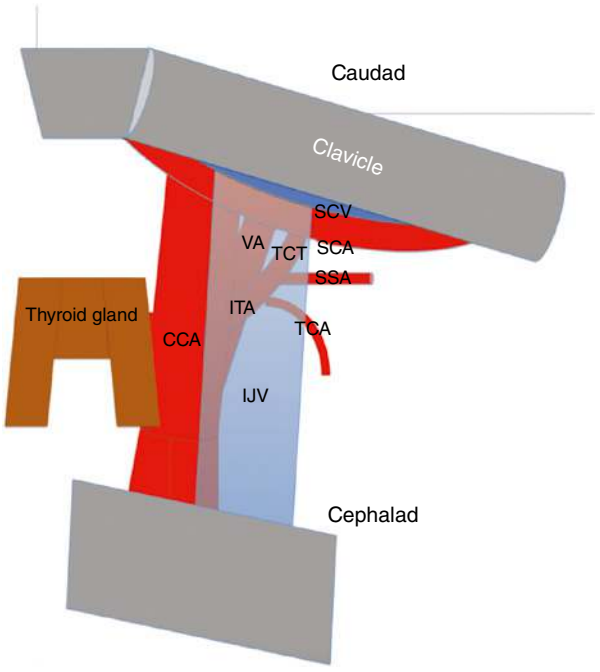


Figure 13.8 Schematic of the anatomic relations among the common carotid artery (CCA), internal jugular vein (IJV), vertebral artery (VA), thyrocervical trunk (TCT), subclavian artery (SCA), subclavian vein (SCV), suprascapular artery (SSA), transverse cervical artery (TCA), and inferior thyroid artery (ITA).

Technique. For right-side IJV puncture, the ultrasound instrument may be placed on the right side of the patient. Before catheterization of the IJV, the pulsation of the carotid artery should be confirmed by palpation at the middle of the patient's neck. (Figure 13.11A2). Under the IJV, the pulsatile vessel, possibly the vertebral artery, can sometimes be felt to be obviously different from the carotid artery. The relationship between the vertebral artery and the IJV, in addition to the relationship between the carotid artery and the IJV, should be assessed by ultrasound imaging out of plane (Figure 13.11B1) and in plane (Figure 13.11B2). Images of other arteries around the IJV, such as the subclavian artery, thyrocervical trunk (Figure 13.10A), transverse cervical artery (Figure 13.10B), and inferior thyroid artery, are sometimes obtained. After disinfecting the puncture site, place the probe with sterilized cover perpendicular to the IJV using the swing or sweep technique to keep the probe perpendicular to the vein in the ultrasound-guided, out-of-plane technique. Before puncturing the skin under real-time ultrasound guidance, depress the targeted skin surface puncture point above the IJV with the tip of a dull, metal, sterilized instrument, such as a hemostat, to simulate puncture without puncturing the skin surface. Obtain an ultrasound image of the intended needle on the screen to confirm the accurate point of puncture at the midpoint between the outer and inner wedges of the IJV. The IJV should be continuously kept in the middle of the monitor without moving the probe to the side and maintaining its perpendicular position. The tip of a 24 ga angiocatheter may be placed at a precalculated angle to the skin (Figure 13.12).

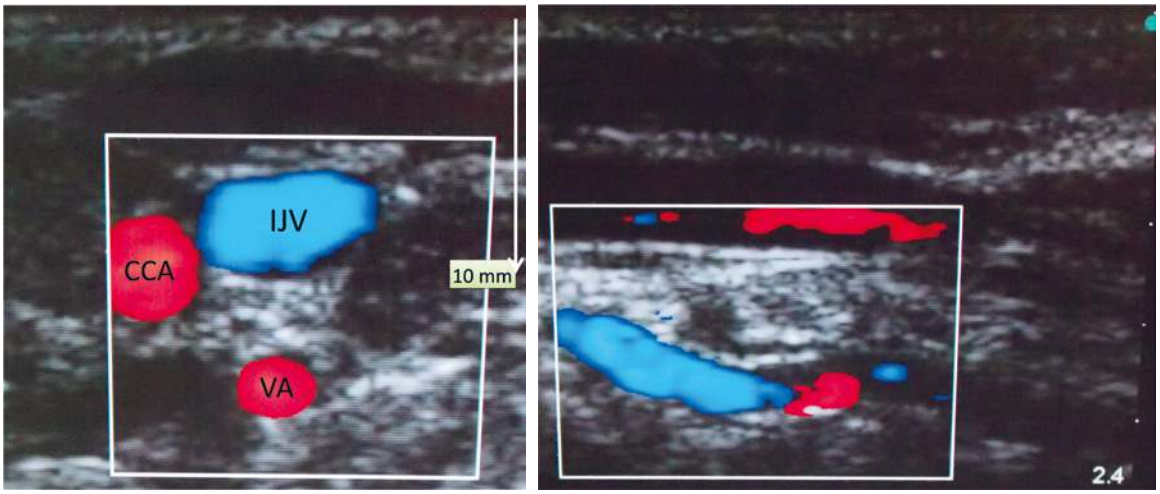


Figure 13.9 Out-of-plane (A) and in-plane (B) Doppler color flow imaging of the common carotid artery (CCA), internal jugular vein (IJV), and vertebral artery (VA) in a 5-month-old infant.

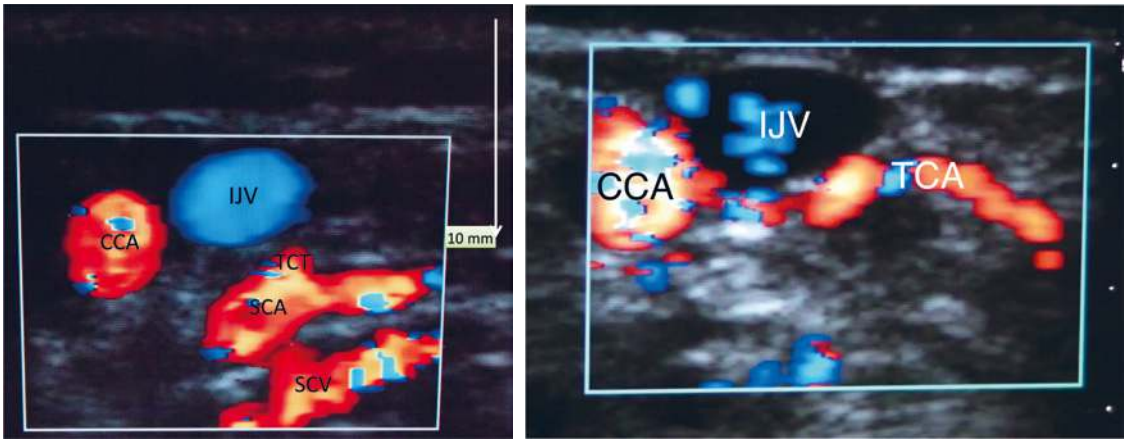
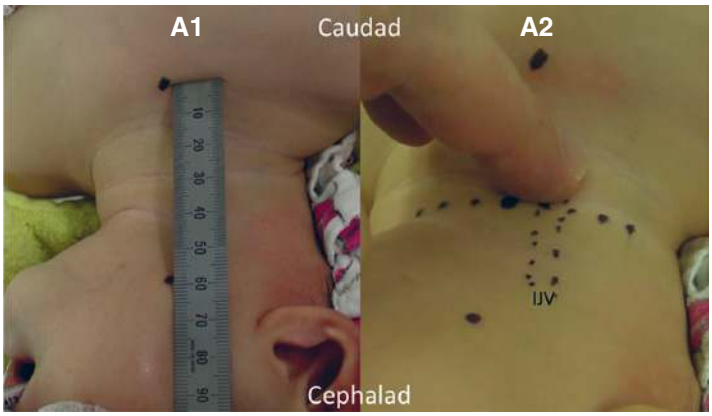


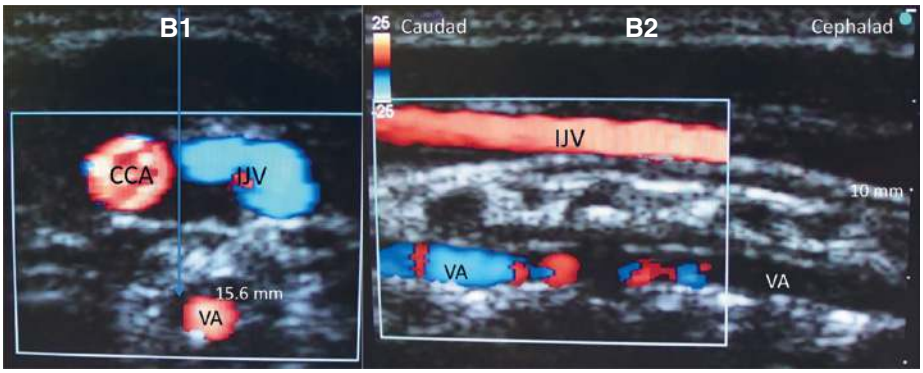
Figure 13.10 Out-of-plane Doppler color-flow imaging of the neck vessels. (A) Out-of-plane Doppler color-flow imaging of the common carotid artery (CCA), internal jugular vein (IJV), subclavian artery (SCA), thyrocervical trunk (TCT), and subclavian vein (SCV) in a 5 month-old infant. The image was obtained near the clavicle. (B) Imaging of the CCA, IJV, and transverse cervical artery (TCA) in an 11-month-old infant. The image was obtained at a site slightly caudal from the mid-portion of the neck, above the clavicle.

Puncture the skin and visualize the tip of the needle at the center of the anterior wall of the IJV. The probe can be moved along the IJV, maintaining it perpendicular to the vein. Bear in mind that the probe is 12–16 mm thick in its short axis, which hinders the proper advancement of the needle. By inserting the needle 3–5 mm below the skin and then placing the probe near the needle, one can avoid hindrance by the probe – considering the relationship between the depth from the skin and the angle of the probe. Continue observing the tip of the needle on ultrasound throughout the procedure. The tip can be observed at the anterior wall of the IJV (Figure 13.11C1). Two bright echo enhancements of the tip may be seen inside the IJV (Figure 13.11C2). Additional needle advancement is necessary to penetrate the anterior wall with the outer catheter. The distance from the tip of the inner needle and the tip of the outer catheter is approximately 2 mm for a 24 ga angiocatheter. After obtaining dark-colored non-pulsatile blood return (Figure 13.11D1), the slightly curved guidewire should be carefully inserted into the IJV (Figure 13.11D2). When any resistance is encountered during guidewire advancement, advancement must be stopped, and the blood return should be reconfirmed. The course of the guidewire should be confirmed by ultrasound (Figure 13.12) or fluoroscopic imaging before inserting dilators. If there is no blood return, the needle should be withdrawn, and re-puncture is required. If inadvertent artery puncture occurs, press on the puncture site for several minutes to aid in hemostasis. After smooth insertion of the guidewire, the outer catheter must be advanced carefully into the IJV (Figure 13.11D3), and dark-colored blood return should be reconfirmed (Figure 13.11D4) to avoid artery catheterization. As discussed earlier, once the catheter is placed in the vein, a short extension tube can be connected to

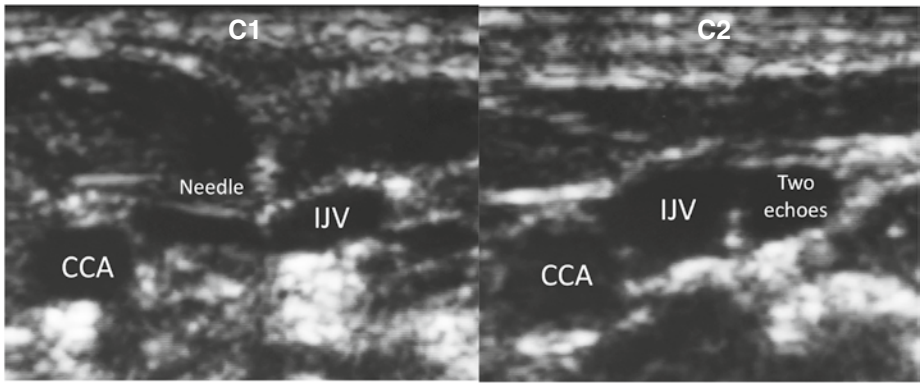
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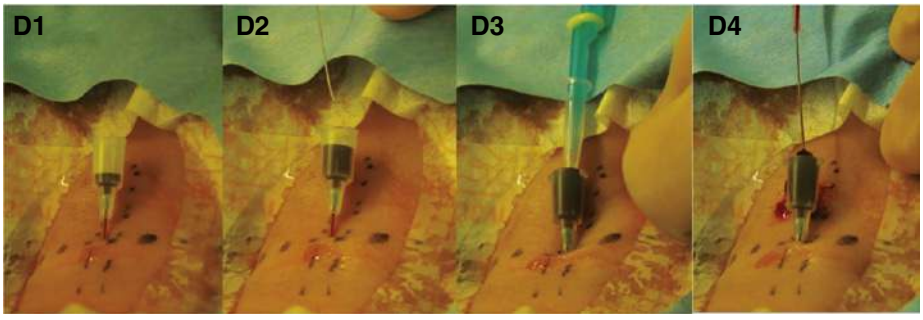
(A)



(B)



(C)



(D)

Figure 13.11 Internal jugular vein (IJV) puncture under real-time ultrasound guidance. (A) The distance from the clavicle and the angle of the mandible is approximately 60 mm (A1). The common carotid artery (CCA) and the IJV are outlined and palpated (A2). (B) The CCA and the IJV are visualized by ultrasound Doppler color flow out-of-plane (B1) and in-plane (B2) (VA, vertebral artery). The tip of the angiocatheter is advanced into the IJV and positioned at the anterior wall of the IJV (C1). Two bright echo enhancements are seen at the tip of the needle (C2). Blood return is obtained through the 24 ga angiocatheter; dark-colored and non-pulsatile blood return is obtained (D1). Blood return has increased (D2). The guidewire is inserted and the needle is advanced (D3). We always suspect that the guidewire might possibly advance into arteries behind the IJV. Dark-colored blood return is obtained again; this blood is believed to be venous (D4).

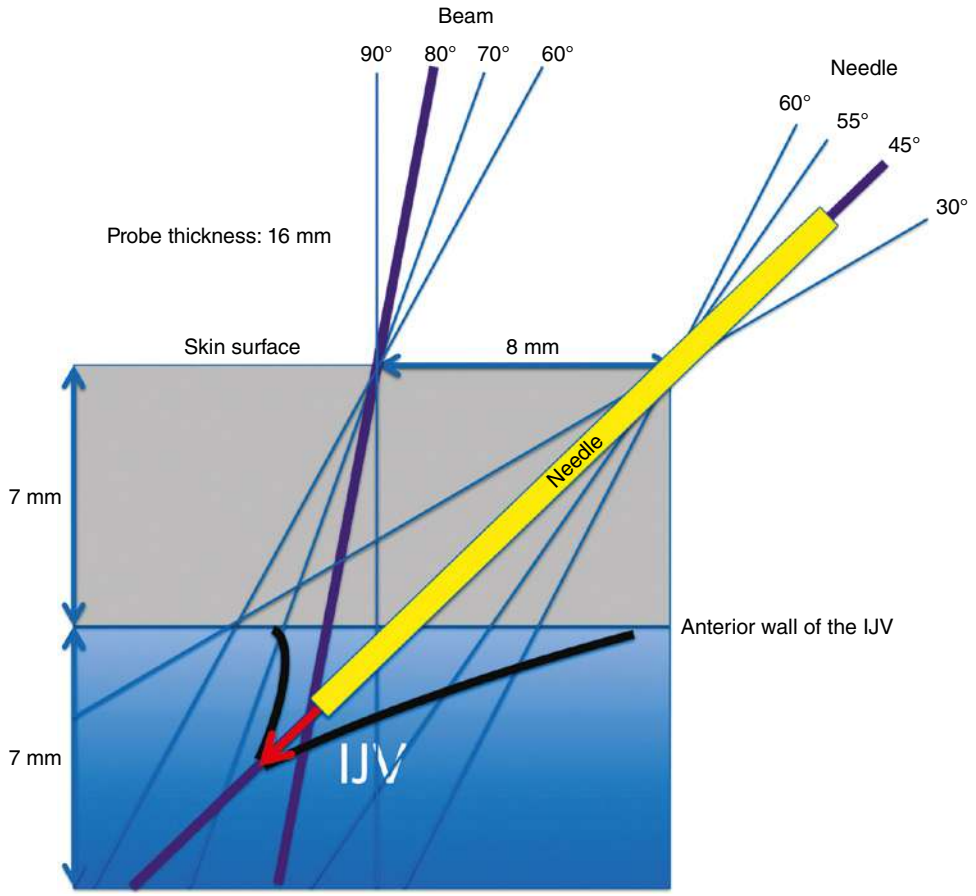


Figure 13.12 The relationship between ultrasound beam and needle angles. To effectively obtain an image of the needle tip on the monitor, the ultrasound beam and needle angles should be as parallel to each other as possible. More than an 8 mm distance between the center of the needle and the puncture site on the skin surface is required when a 16 mm-thick ultrasound probe is used. When the internal jugular vein (IJV) with a 7 mm anterior-posterior length is located 7 mm beneath the skin, the optimal beam angle is 70°–80° to obtain a good image of the needle tip in the IJV while advancing the needle at a 45° angle to the skin. When the beam angle is 60° to the skin, the optimal angle of the needle is approximately 30° angle to the skin. Adjust the angle according to the probe thickness and IJV depth.

the catheter, which can then be used to verify venous access. Carefully insert the dilator along the guidewire so as not to damage vessels or the guidewire while confirming the smooth movement of the guidewire. If any resistance is felt during dilator insertion, stop the advancement and confirm the smooth movement of the guidewire in the IJV. Use fluoroscopy if necessary. Guidewire deformation may suggest complications such as vein or artery perforation. Confirmation of an in-plane, long-axis image of the guidewire (Figure 13.13) is useful in most patients [100]. Careful insertion of dilators is mandatory to avoid serious complications.

Ultrasound-guided SCV puncture

Central catheters can be placed via the SCV under ultrasound guidance [82, 101–103]. The SCV, in addition to the IJV, carotid artery, clavicle, and its shadow can be identified by transectional scanning (Figure 13.14). An ultrasound-guided supraclavicular approach for SCV puncture is now possible for central venous catheterization in small infants, offering all of the advantages of SCV catheterization without the risk of "pinch-off" syndrome [100]. Supraclavicular ultrasound-guided catheterization of the SCV in the pediatric and neonatal ICU appears to be a promising technique in the emergency context [101]. It is safe and reliable, with few early complications. Furthermore, owing to the low level of sedation needed for its placement, it does not compromise the airway of the patient.

Technique. The principle of the ultrasound-guided approach for SCV catheterization is to place the ultrasound probe at the supraclavicular level to obtain a longitudinal view of the SCV and to gain access to the vein via the usual infraclavicular route for cannulation. Place the ultrasound probe on the mid-portion of the neck. Slide the probe caudally, and lean 45°–60° to the skin. Both the subclavian artery and vein are first visualized transversely under the IJV, and then a longitudinal view of the brachiocephalic vein, beginning at the junction of the IJV–SCV, can be obtained. After reaching the IJV–SCV junction, rotate the ultrasound probe laterally and caudally to obtain longitudinal images of the SCV and the brachiocephalic vein. With in-plane imaging, place the needle under the probe to simultaneously observe the SCV and the needle tip. Puncture the mid-portion of the venous anterior wall. After obtaining dark-colored venous

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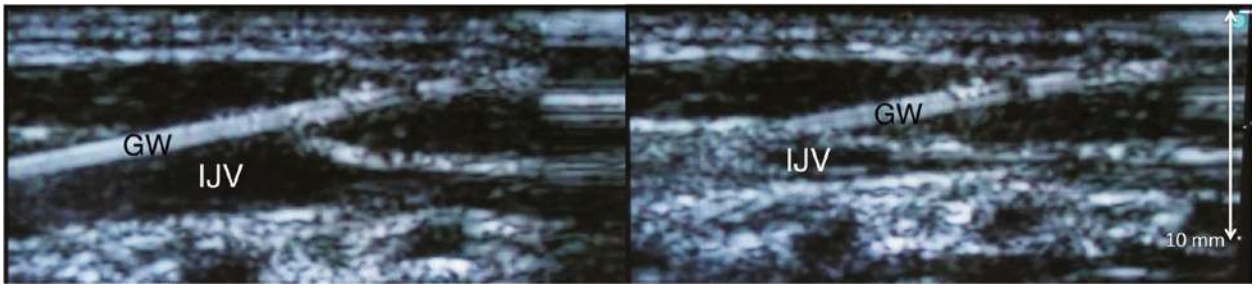


Figure 13.13 In-plane ultrasound images of the guidewire (GW) in a 6-month-old infant. (A) The GW is seen in the internal jugular vein (IJV). (B) The IJV is compressed, and the inner portion of the IJV cannot be seen.

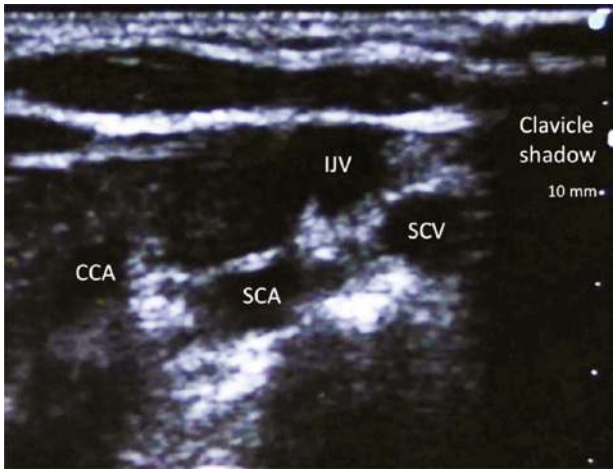


Figure 13.14 The subclavian vein (SCV), internal jugular vein (IJV), common carotid artery (CCA), and clavicle. In a 5-month-old infant, the SCV, IJV, CCA, and the clavicle and its shadow can be identified by transectional scanning. SCA, subclavian artery.

blood, insert the guidewire, and advance the procedure as for ultrasound-guided IJV catheterization.

Ultrasound-guided brachiocephalic vein puncture

Ultrasound-guided supraclavicular catheterization of the brachiocephalic vein is now possible for central venous line placement in small children. Place the broadband linear array ultrasound probe in the supraclavicular region to obtain a longitudinal view of the brachiocephalic vein, beginning at the junction of the IJV and SCV. Using the in-plane technique, direct the needle under ultrasound guidance into the brachiocephalic vein. This provides good needle guidance with no disturbing ultrasound shadow caused by bony structures. The success rate of central catheterization via the brachiocephalic vein in children appears to be very high [104].

Ultrasound-guided EJV puncture

The EJV can often be seen on the lateral side of the patient's neck. Ultrasound imaging facilitates confirmation of its course; however, safety and success rates of the conventional surface anatomic landmark technique and the ultrasound-guided technique are similar for inexperienced trainees [105].

Ultrasound-guided FV puncture

The FV is an optimal site for ultrasound guidance, and the infection rate does not appear to be high, as mentioned earlier.

Technique. As described earlier, the patient is positioned with a rolled towel under the hips for moderate extension. For right-side FV puncture, place the ultrasound monitor on the patient's left side. The practitioner may stand on the patient's right side in order to see the monitor over the patient. Check to ensure that the femoral artery and FV are 1–2 cm from the inguinal ligament by palpation, and then use the ultrasound. The femoral artery is located on the left, lateral side and runs toward the practitioner with a pulsatile, Doppler red-colored flow. The FV is located on the right medial side and runs away from the practitioner with a non-pulsatile, blue-colored flow. Before insertion, check the course of the vessels, and place the probe perpendicular to the FV using the swing or sweep technique. The FV in children is located 7–22 mm from the skin [106], which is usually deeper than the IJV and enables one to obtain an ultrasound image more easily than for the IJV. After sterilization, puncture the skin 1–2 cm from the inguinal ligament according to the probe thickness as described for ultrasound-guided IJV puncture.

Ultrasound-guided arterial catheterization

Ultrasound-guided radial artery catheterization can be useful even in neonates and infants. Radial artery insertion by ultrasound is often selected after the failure of radial artery catheterization by palpation. Ultrasound can visualize the course of the small radial artery even in difficult cases in neonates and infants. Highly successful catheterization can often be achieved when ultrasound images of the tip of the puncture needle and the radial artery are obtained in the same screen under the skin. Ultrasound guidance can improve the success rate of artery catheterization in infants. Fewer attempts with the ultrasound technique are required compared with the traditional technique [107, 108]. Ultrasound-guided radial artery catheterization in infants and small children can provide a greater chance of success at the first attempt compared with the Doppler-assisted technique [109].

Serious complications, such as permanent ischemic damage, are infrequently observed in with ultrasound-guided arterial catheterization for perioperative and intensive care monitoring. However, ultrasound guidance may not facilitate faster catheterization of the radial artery in children.

Technique. Prepare the patient's hand position as described for the palpation method (see earlier). Before catheterization of the radial artery, the course of the radial artery can be palpated and then confirmed with ultrasound Doppler color flow. Once the radial artery has been located by ultrasound, the pulsation of the radial artery becomes easier to capture visually on the monitor, even in neonates and infants. After disinfecting the skin, place the probe with sterilized cover directed perpendicular to the radial artery using the swing or sweep technique to keep the probe directed perpendicular to the artery using the ultrasound-guided, out-of-plane technique. Obtain the ultrasound image of the intended needle on the screen to confirm the accurate point for puncture (Figure 13.15). The radial artery image should be continuously maintained in the middle of the monitor. When bright-colored, brisk flashback is obtained from the inner needle while puncturing, advance the catheter 1–2 mm to enter the artery. When the artery is transfixed, withdraw the needle and gently withdraw the catheter until brisk flashback is observed. The catheter can then be advanced into the artery. Alternatively, when

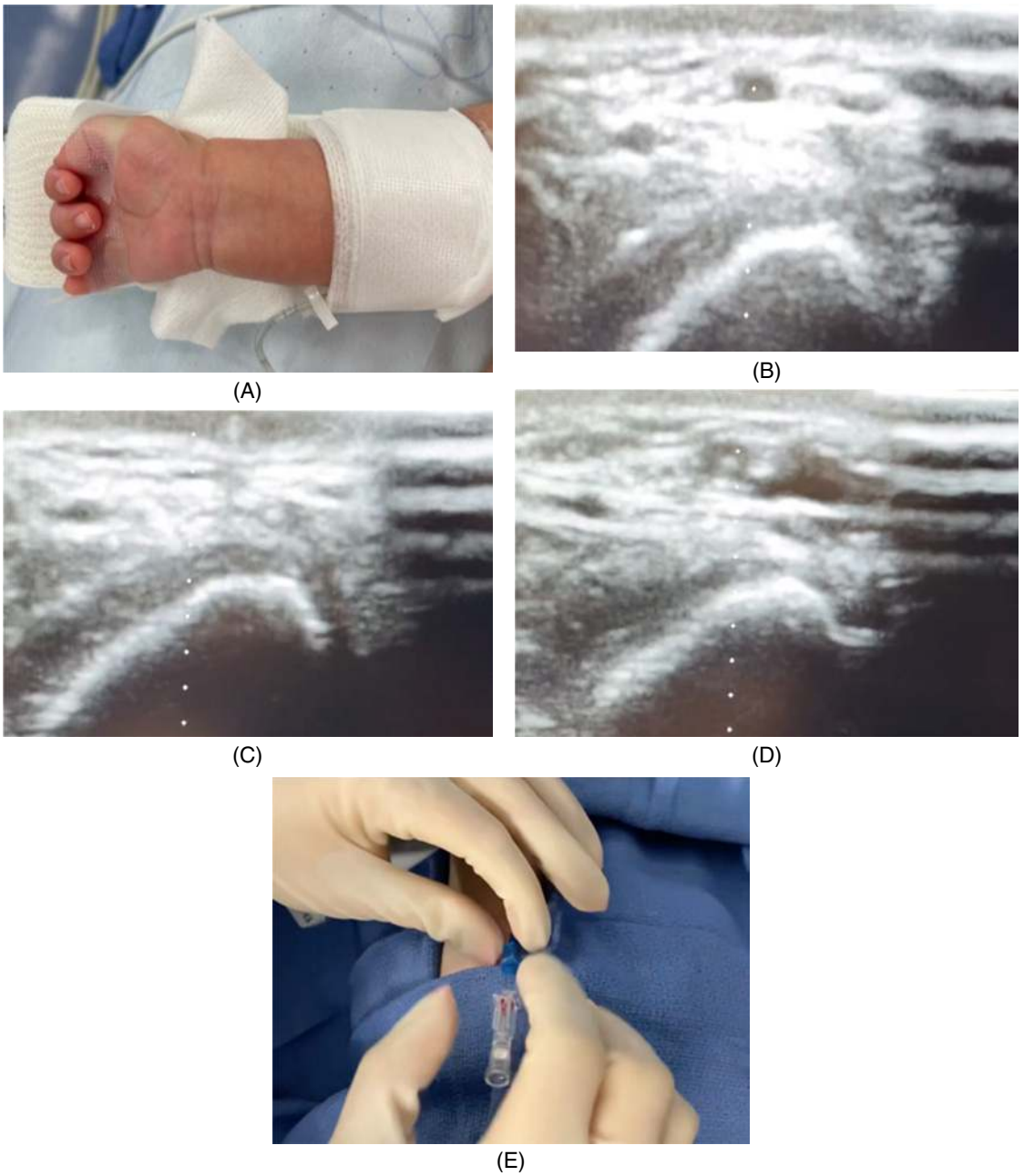


Figure 13.15 (A–E) Ultrasound-guilded radial arterial cannulation. See text for details.

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the tip of the needle is visualized inside the artery at the center, the needle and catheter together can be advanced fully into the artery, keeping the tip of the needle in ultrasound view in the center of the artery during advancement. There is no need to watch for a flashback in the hub of the needle with this method. This technique has the advantage of lessening risk of puncture or damage to the back wall of the artery. Remove the needle when the catheter is advanced to the hub. Connect the catheter to the pressure tubing, paying close attention to avoiding air in the line. Place a cushion between the skin and the catheter with the connector to avoid skin necrosis and cover the catheter with the connector with sterile tape. We often obtain non-pulsatile, bright-colored blood from a 24 ga angiocatheter just after catheterization. Pulsatile blood inside the connected needle can be obtained after connecting to the pressure monitor line. Because of the small radial arterial size in small children, subcutaneous nitroglycerin injection (0.5 μg/kg in 0.5 mL saline) prior to the ultrasound guided radial arterial access significantly increased the diameter of the radial artery. This led to an increase in the success rate of the first attempt, a decrease in the number of cannulation attempts, and cannulation related complications [110].

An alternative ultrasound technique is to image the radial artery in the longitudinal plane and visualize the entire length of the needle and catheter inserted into the vein [111] (Figure 13.16). A controlled study of short axis vs. long axis ultrasound imaging for radial artery catheterization in 97 infants and children revealed no difference in success rate (94% short axis vs. 98% long axis), time to cannualtion, or complications. The incidence of puncturing the posterial arterial wall was higher in the short axis group; (96 vs. 18%, $p < 0.001$).[112]

KEY POINTS: ULTRASOUND-GUIDED VASCULAR ACCESS

- Ultrasound-guided vascular access can increase the success rate of catheter insertion and decrease complication rates associated with catheterization.
- The use of real-time, ultrasound-guided IJV puncture increases first-insertion success, reduces access time, has greater overall success, and reduces inadvertent arterial puncture.
- An ultrasound-guided supraclavicular approach for SCV puncture is now possible for central venous catheterization in small infants.

Percutaneous PA catheterization

Although multi-lumen, flow-directed PA catheters have long been used widely in adult practice, great controversy has arisen during the past several decades [113–117], and their use has decreased significantly, especially in children, and become rare in infants [118]. The Pulmonary Artery Catheter Consensus Conference published a consensus statement regarding the use of PA catheters in pediatric patients [119]. It recommends that PA catheters should only be used in selected patients, such as those with pulmonary hypertension and shock refractory to standard fluid resuscitation and vasoactive agents [120]. In patients undergoing congenital heart surgery, PA pressure monitoring may be indicated for reasons related to the cardiac condition of the patient or the nature of surgery. Patients undergoing surgery on left-sided lesions and who do not have intracardiac shunting, those who are at risk of left ventricular dysfunction, and those with pulmonary hypertension may have indications for PA catheterization. Examples of surgical procedures include aortic surgery, aortic valve surgery or replacement, subaortic resection or myomectomy for hypertrophic cardiomyopathy, and mitral valve repair or replacement. However, PA catheterization has a limited role, if inserted percutaneously, for several reasons. First, adequately sized catheters and sheaths are not available in sizes small enough for the smallest pediatric patients. Secondly, most of these patients have intracardiac shunting, and standard thermodilution cardiac output (CO) measurements, and mixed venous oxygen saturation (SvO_2) measurements are unreliable. In addition, a PA catheter in the right side of the heart may interfere with the surgical field. Thus, when PA pressure or SvO_2 monitoring is indicated, transthoracic PA lines placed under direct visualization at the end of CPB surgery are the most commonly used approach.

Percutaneous PA catheterization is used less frequently in children than in adults, mainly due to greater difficulty in gaining access because of patient size and the unavailability of small-sized PA catheters; however, if the patient is large enough to insert a 5 or 6 Fr introducer sheath in the FV or IJV, percutaneous PA catheter insertion may be feasible.

Pulmonary artery catheters are available in various sizes (4–8 Fr) for different functions, such as pressure monitoring, thermodilution measurement of intermittent or continuous CO, continuous measurement of venous saturation, and cardiac pacing. Commonly used sizes for pediatric patients are 4 Fr (non-balloon-tipped, two-lumen, oximetry catheter), 5 Fr (balloon-tipped, four-lumen, thermodilution catheter), 5.5 Fr (balloon-tipped, four-lumen, oximetry and thermodilution catheter), and 7.5 and 8 Fr (balloon-tipped, three-lumen, oximetry and thermodilution catheter).

It must be stressed that a PA catheter should be used as a diagnostic and hemodynamic monitoring tool and not as a therapeutic intervention; interpretation of the data derived from a PA catheter and subsequent management decisions are crucial to benefit patients fully, requiring attending physician-level expertise. Efficacy studies supporting the use of PA catheterization in children undergoing congenital heart surgery are scarce in the existing literature. Therefore, risks incurred by PA catheter placement should be well taken into account.

Technique. The previously mentioned consensus statement, as well as the guidelines set by the American Society of Anesthesiologists task force, recommends that PA catheters should only be used by suitably experienced personnel to minimize complications, thus requiring adequate supervision throughout the procedure [121] The selection of PA catheter should be based on clinical need and patient size. To obtain maximal benefits, a PA catheter with oximetry and thermodilution CO measurement capabilities is desirable. Commercially available catheters equipped with these

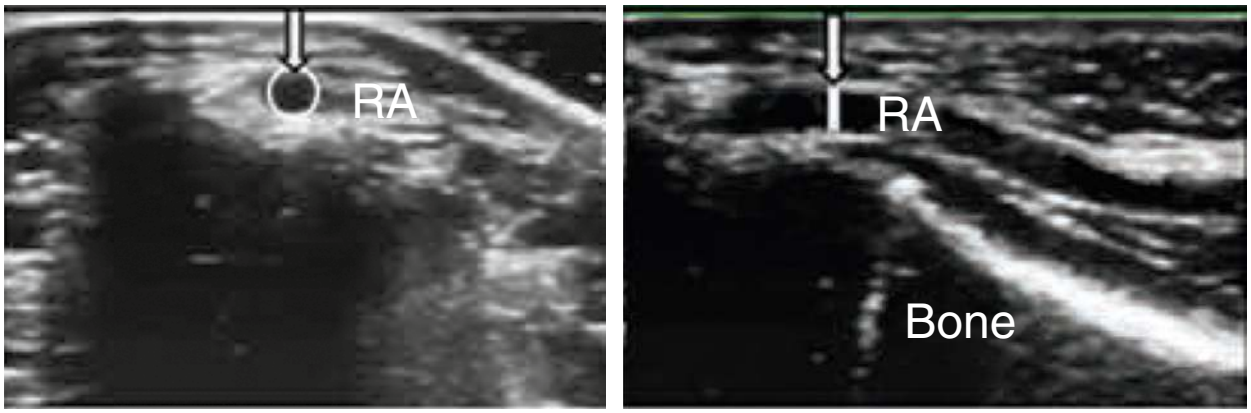


Figure 13.16 (A) Radial artery in short axis view. (B) radial artery in long-axis view. (Source: Kim et al [111]. Reproduced with permission from Wolters Kluwer Health, Inc.)

functions are 5.5 or 7.5 Fr in size and thus require a 6 or 8 Fr introducer sheath, respectively. A 5.5 Fr PA catheter should be used in patients up to approximately 40 kg in weight. Because of the direct path and curvature of the catheter, appropriate sites of insertion are the right IJV, left SCV, and FVs.

After full barrier precautions are taken and using the Seldinger technique following guidelines described earlier for percutaneous central catheter insertion, insert an introducer sheath into a central vein. The balloon integrity should be tested before insertion by inflating the recommended volume of air. Insert a flexible sterile sleeve before placement to protect the PA catheter outside the body and to allow for sterile repositioning later. Connect, flush, and calibrate the PA and CVP ports before insertion. Advance the catheter as far as the RA with the balloon deflated, then inflate the balloon and advance the catheter into the PA while observing the pressure tracing. The catheter's advancement toward the tricuspid valve is signified by enlarging V waves on the CVP tracing. The catheter passes through the tricuspid valve during diastole and the characteristic RV trace becomes visible on the PA tracing, with no dicrotic notch and moderate diastolic pressure. Hasten advancement of the catheter through the RV because of the propensity for dysrhythmias. The diastolic pressure increases and the dicrotic notch becomes apparent as the catheter tip passes through the pulmonary valve. Gently advance the catheter until a pulmonary capillary wedge pressure (PCWP) tracing is obtained, at which point the balloon should be deflated so that the PA tracing returns. It may be necessary to reduce or remove any redundant length or loop in the RA or RV by slowly withdrawing the catheter 1–2 cm. The balloon can then be reinflated to determine the minimum inflation volume necessary to obtain a wedge pressure tracing. The best position for the catheter tip is where the full or near-full inflation volume (0.5–1.5 mL) produces a wedge pressure tracing. Advancement of the catheter to the PA should be relatively rapid because prolonged manipulation may result in loss of catheter stiffness, thereby causing coiling in the RV or difficulties in catheter advancement. When difficulty advancing the catheter through the pulmonary valve is encountered, counter-clockwise rotation of the catheter, along with positioning the patient with the right side down, may result in successful placement. Alternatively, TEE may be used to visualize and guide the PA catheter. The PA pressure should always be monitored with the waveform displayed on the monitor so that migration of the catheter into the distal PA or RV can be detected immediately. Leaving the catheter in the wedged position undetected can lead to particularly serious complications such as PA rupture or pulmonary infarction. The catheter should be withdrawn several centimeters during the bypass period to reduce the risk of PA perforation.

Specific information that can be gathered with regular PA catheters includes PA pressure (systolic, diastolic, and mean), PCWP, RA pressure, mixed venous gases, and CO by thermodilution. Measurement of the PCWP is important because it is a reasonable estimate of left atrial pressure (LAP), which in turn is an estimate of left ventricular end-diastolic pressure (LVEDP). The assumption that PCWP reflects LAP is only valid if patency of vascular channels between the distal port of the PA catheter and the left atrium is ensured. This will occur only in dependent portions of the lung (West's zone 3), where pulmonary venous pressure exceeds alveolar pressure. Fortunately, with the patient in the supine position, a large portion of the lung is functioning in zone 3, and PA catheters will preferentially float into zone 3. To avoid erroneous readings, the PCWP should be measured at end expiration. The PCWP may not accurately reflect LVEDP in the presence of pulmonary venous or arterial hypertension, mitral valve disease, or positive end-expiratory pressure. The LVEDP is an index of left ventricular end-diastolic volume, the classic measure of left ventricular preload. The relation between left ventricular end-diastolic pressure and volume is best described by the left ventricular compliance curve, which is non-linear and is affected by many factors, such as ventricular compliance. Because TEE can provide more precise information regarding ventricular volume status, the usefulness of measuring PCWP becomes questionable.

Cardiac output can be measured with the standard thermodilution technique. In brief, a thermodilution PA catheter is connected to a CO monitor, a known amount of solution (injectate) of known temperature is rapidly injected into the proximal lumen of the catheter, this cooler-than-blood temperature solution mixes with the surrounding blood, the

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temperature is measured downstream in the thermistor on the PA catheter, and a decrease in temperature is recorded. The magnitude of the temperature change depends on the amount of blood that mixes with the injectate, and hence CO. The CO computer constructs a time–temperature curve to calculate CO from the area under the curve (AUC). When CO is low, more time is required for the temperature to return to baseline, producing a larger AUC. In contrast, with high CO, the injectate is carried more quickly through the heart, and the temperature returns to baseline faster, producing a smaller AUC. Thus, CO is inversely proportional to the AUC. Several factors may affect bolus CO determination: inaccurate temperature and volume of the injectate, rapid intravascular volume infusion during measurement, timing during the respiratory cycle, inaccurate computation constant, and thermal instability during the immediate post-bypass period. In addition, the presence of an intracardiac shunt can lead to erroneous CO values. For example, a left-to-right intracardiac shunt will cause recirculation of the injectate and create a larger AUC (decreased peak height and slower return to baseline), providing an erroneously low CO reading. A right-to-left shunt will have the opposite effect, providing an erroneously high CO reading. Therefore, the presence of an intracardiac shunt precludes the use of the thermodilution method to calculate CO. Technologic advances have produced PA catheters for continuous thermodilution CO monitoring using thermal indicators. Whereas the intermittent bolus technique uses cold injectate as the indicator, the new technology uses small energy impulses (warming of blood), which are emitted from a thermal filament directly into the bloodstream as the indicator; no fluid injection is required. These pulses of thermal energy emitted in a random on-off pattern change blood temperature, which is then detected by the thermistor at the tip of the PA catheter. Using a proprietary algorithm to analyze the thermal signal measured at the thermistor, a time–temperature curve is generated to calculate CO from the AUC. Typically, the displayed value for CO is updated every 30 seconds and represents the average CO over the previous 3–6 minutes. In this sense, this technology provides continual, frequently updated CO values.

Once CO is measured, systemic and pulmonary vascular resistances can be calculated. According to Ohm's law, vascular resistance equals the pressure drop (pressure difference between the upstream and downstream circulation) divided by blood flow (CO). This equation is based on the assumptions that blood flow is steady-state, continuous, and laminar, and blood vessels are rigid conduits. This may be unrealistic for the pulmonary circulation, because pulmonary blood flow may cease at end diastole and pulmonary vessels are distensible [122]. Therefore, pulmonary vascular resistance calculated by PA catheters may have limited value, although it is widely used; interpretation should be performed with caution. Other hemodynamic parameters [123–128] that can be calculated by PA catheter are listed in Table 13.6.

In addition to calculated hemodynamic variables, PA catheters can also provide important information regarding oxygen delivery and consumption, which may be used to guide therapy in critically ill children with low-CO syndrome. Because the arterial oxygen content is relatively constant under conditions of regular gas exchange, the major reflection of alterations in tissue oxygen extraction is SvO_2 [129]. If oxygen delivery is compromised to the periphery, tissues will increase their extraction of oxygen to compensate for reduced oxygen delivery. This will result in a decrease in SvO_2. Therefore, SvO_2 is an indirect indicator of the adequacy of tissue oxygenation, or a reflection of the balance between oxygen requirement and oxygen delivery. The relation between SvO_2 and CO can be shown by the modified Fick equation:

$$SvO_2 = \frac{SaO_2 - VO_2}{1.34 \times Hb \times CO}$$

where SaO_2 is the arterial oxygen saturation, VO_2 is the rate of oxygen consumption, and Hb is the hemoglobin concentration. From this equation, it is apparent that SvO_2 varies directly with CO, Hb, and SaO_2 and indirectly with metabolic rate (oxygen consumption).

A fiberoptic-equipped PA catheter allows for continuous monitoring of SvO_2 to guide timely therapeutic interventions during the perioperative period. Interpretation of SvO_2 may become difficult under conditions of intracardiac shunt, peripheral arterial venous shunt, sepsis, and cirrhosis.

KEY POINTS: PULMONARY ARTERY CATHETERIZATION

- A PA catheter should only be indicated in selected patients with CHD. Experienced physicians should directly supervise PA catheterization and its maintenance to avoid serious complications and erroneous interpretation of the data.
- Available sizes of PA catheter are a limiting factor for percutaneous insertion in children.
- In addition to hemodynamic parameters derived from the PA catheter, oxygen wellness should be calculated to direct therapy in ill children with low CO.

Interpretation of intravascular pressure waveforms

The information derived from intravascular catheters exceeds that of merely monitoring an absolute number; it is enhanced by observing the waveforms themselves. Accurate interpretation of the waveforms requires some understanding of the mechanical and electronic technical components of pressure monitoring. Pressure waves in the arterial and venous systems represent the transmission of forces generated in the ventricles. Measurement of these forces requires their transmission to a device that converts mechanical energy into electrical signals, which are processed and displayed. A system for intravascular pressure monitoring consists of intravascular catheters, fluid-filled tubing, connectors, transducers, amplifiers, and display devices. Understanding this system is a prerequisite for interpreting pressure waveforms. Although the use of commercially available, disposable transducer kits is common practice these days, the shortest possible, large-bore, stiff, plastic tubing should be tailored to the patient's size.

Table 13.6 Normal values of hemodynamic and oxygen parameters

	Formula	Neonate/infant	Children			Adolescent/Adult	Unit	Source
			Toddler	Preschool	School Aged			
HR		100–180	93–160	70–140	62–140	60–100	min^{-1}	[119–121]
LVCO	HR × SV	0.8–5.0	1.7–3.8	1.3–5.4	3.2–6.3	4.0–8.0	L/min	[120]
LVCI	LVCO/BSA	2.0–4.0	3.5–6.5	3.0–7.1	3.3–6.9	2.8–4.2	$L/min/m^2$	[120, 122]
RVCI	RVCO/BSA	3.0–4.4		3.6–5.8			$L/min/m^2$	[121]
LVSV	LVEDV – LVESV or CO/HR	5–13	18–32	13–60	47–65	60–130	mL/beat	[120, 121, 123]
LVSVI	LVSV/BSA	40–75	31–55	37–70	42–76	30–65	$mLbeat/m^2$	[121, 122]
LVEF	LVSV × 100/LVEDV	45–81		46–71	47–77	47–78	%	[120, 123, 124]
RVEF	RVSV × 100/RVEDV	59–73	39–63	55–73			%	[118, 121, 122]
LVSWI	(MAP – PCWP) × SVI × 0.0136	20–40		30–62		45–60	$g/beat/m^2$	[120]
SVR	(MAP – CVP) × 80/CO	2,800–4,000		1,200–2,800		800–1,200	$dyne\text{-}sec/cm^5$	[120, 122]
PVR	(PAP – PCWP) × 80/CO	<2,000–3,200		<40–320		<250	$dyne\text{-}sec/cm^5$	[122]
RVEDV		31–47		57–83		100–160	ml	[121]
Arterial O2 content (CaO2)	$1.34 \times Hb \times SaO_2 + 0.0031 \times PaO_2$	15–18		16–18		18–20	mL/dL	[122]
Mixed venous O2 content (CvO2)	$1.34 \times Hb \times SvO_2 + 0.0031 \times PvO_2$	11–14		12–14		13–16	mL/dL	[122]
Arterial-venous oxygen difference	$CaO_2 - CvO_2$	4–7		4–6		4–5.5	mL/dL	[122]
Pulmonary capillary O2 content (CcO2)	$1.34 \times Hb \times SCcO_2 + 0.0031 \times PcO_2$	16–19		17–19		19–21	mLdL	[122]
Pulmonary shunt fraction (Qs/Qt)	$100 \times (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$			2–8			%	[122]
O2 delivery index (DO2I)	$CO \times CaO_2 \times 10/BSA$	450–750		450–700		450–640	$mL/min/m^2$	[122]
O2 consumption index (VO2I)	$(CaO_2 - CvO_2) \times CI \times 10$	150–200		120–200		85–170	$mL/min/m^2$	[122]

CI, cardiac index; CO, cardiac output; EDV, end-diastolic volume; HR, heart rate; LV, left ventricle; PVR, pulmonary vascular resistance; RV, right ventricle; SV, stroke volume; SVI, stroke volume index; SVR, systemic vascular resistance; SWI, stroke work index

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Minimization of the number of stopcocks and connections will improve the fidelity of the transmitted pressure wave [130]. It is imperative that the tubing system be thoroughly flushed before use to eliminate air bubbles or clots. In addition, it is important to recalibrate at the RA level (mid-axillary line) periodically to correct for transducer "drift." Ringing and damping are two common sources of erroneous data acquisition from pressure monitoring and are associated with problems of dynamic accuracy [131–133]. Because a pressure monitoring system has resistance, inertia, and compliance, it can oscillate or "ring," that is, overestimate the systolic pressure and underestimate the diastolic pressure. A system that is ringing (underdamped) results in higher systolic pressure and lower diastolic pressure. In contrast, a damped system provides lower systemic pressure and higher diastolic pressure. In the face of either ringing or damping, mean pressure is preserved and provides an accurate number. If the dynamic response of a system is in question, mechanical devices (e.g. a Resonance OverShoot Eliminator [ROSE™]; Argon Medical Devices, Inc., Plano TX, USA; Accudynamic®, Abbott Critical Care Systems, Abbott Park IL, USA) can be incorporated to alter the resonance frequency and/or damping factor of the transducer system [134, 135]. The resonance frequency can be tested by flushing the system with a pressurized bag of heparinized saline, stopping abruptly, and observing the number and amplitude of oscillations required to return to baseline waveform (dynamic response) [136]. Proper damping is indicated by one oscillation below and one oscillation above the mean before returning to normal.

Arterial pressure waveform

Regular cardiac rhythm and the presence of CO can be confirmed by observation of the waveform on the monitor display. This is useful when prolonged use of electrocautery disturbs the ECG trace. Steep upstroke of the waveform implies good ventricular function, whereas slow upstroke may indicate poor contractility, left ventricular outflow tract obstruction, or peripheral vasoconstriction. The area under the systolic portion of the pressure curve is proportional to the stroke volume [137]. The position of the dicrotic notch is associated with changes in peripheral vascular resistance. In infants, a normal dicrotic notch is found in the upper half of the pressure wave. A dicrotic notch located high on the downslope of the arterial waveform may indicate increased systemic vascular resistance, whereas one located lower on the downslope may indicate low resistance. A low-placed dicrotic notch with a steeper diastolic downslope is also observed in hypovolemic patients. A decrease in both peak systolic pressure and pulse pressure, which is accentuated by positive pressure ventilation, is an early indicator of hypovolemia or cardiac tamponade. Aortic stenosis will result in a pressure waveform with a slow-rising upstroke, delayed peak, and narrow pulse pressure, whereas aortic regurgitation will result in a steep upstroke, bifid peak, widened pulse pressure, and low diastolic pressure. Low diastolic blood pressure can also reflect excessive distal "run-off," as in patients with large patent ductus arteriosus. A sudden increase in diastolic pressure occurs on ligation of the ductus because diastolic run-off into the PA ceases.

The systolic pressure is higher in the more distal arteries due to the wave-reflection phenomenon [138]. As the pressure wave passes down the arterial tree, it is modified by arterial narrowing, loss of arterial elastic tissue, and the addition of reflected waves, until it reaches the distal catheter. With distal progression, pulse wave amplification will produce a higher peaked pressure wave with a slightly higher systolic pressure. This is most pronounced in the arteries of the foot, where the systolic pressure may be 5–15 Torr higher than in the ascending aorta (Figure 13.17) [139]. Diastolic and mean pressures change very little with progression. This concept is important for interpreting arterial pressure tracings. The post-bypass arterial tracing is frequently damped with catheters in small distal arteries (e.g., radial or foot arteries), probably due to vasoconstriction induced by CPB [140]. This usually does not last long after bypass; however, it can be troubling to observe, particularly during potentially critical periods of weaning from bypass. For long and difficult surgeries with long bypass or cross-clamp times, it may be prudent to place catheters in larger, more central arteries (e.g., femoral or umbilical) or to ask the surgeon to measure pressure directly in the aortic root from the aortic cannula immediately after bypass to obtain an accurate arterial pressure.

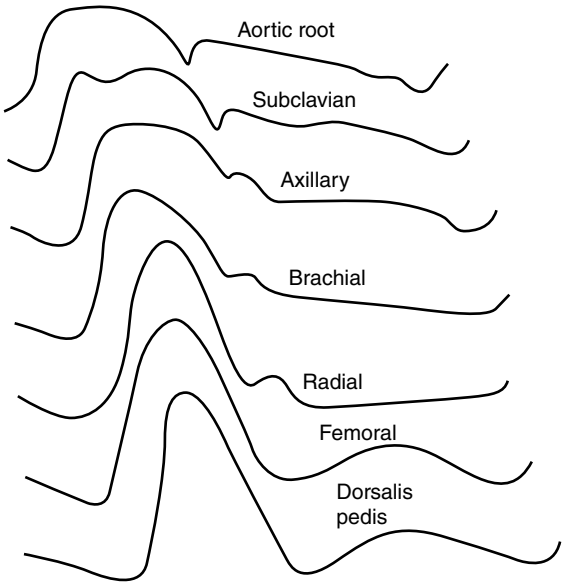


Figure 13.17 Progression of the arterial pressure tracing from the root of the aorta to more peripheral arteries. Pulse-wave amplification produces a higher systolic peak and slightly lower diastolic pressure in the smaller distal arteries, especially the dorsalis pedis. (Source: Reich et al. [139]. Reproduced with permission of Elsevier.)

Failure of arterial pressure monitoring during congenital heart surgery is possible. Reasons for failure can include arterial spasm, kinking or clotting of the catheter, compression of an aberrant right subclavian artery by a TEE probe, or compression of the axillary artery by a sternal retractor. A back-up manual blood pressure cuff should be always available. Alternatively, placement of a femoral artery catheter may be performed by the surgeon.

Central venous and left atrial waveforms

The usual sites of filling pressure measurement are the CVP (right atrial pressure) and LAP. In the presence of normal tricuspid and mitral valves, the CVP and LAP reflect their

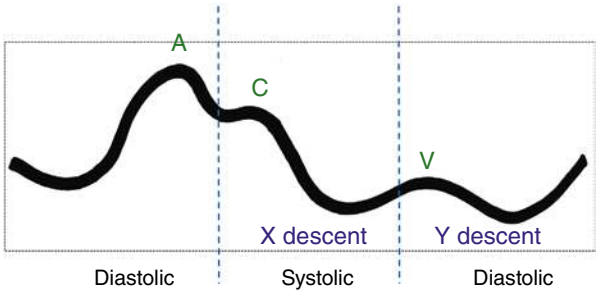


Figure 13.18 Central venous pressure waveform. The A wave represents increased atrial pressure. The C wave represents closure of the tricuspid valve. Downward movement of the ventricle during systolic contraction forms the X descent. The V wave arises from the pressure produced when the blood filling the right atrium comes up against a closed tricuspid valve. Opening of the tricuspid valve in diastole, with blood flowing into the right ventricle, produces the Y descent.

respective ventricular end-diastolic pressures. Normal atrial pressure traces have three positive waves, A, C, and V, corresponding to atrial contraction, closure of tricuspid or mitral valve, and ventricular contraction (Figure 13.18). The right atrial V wave is normally lower in amplitude than the A wave; however, in patients with atrial septal defect, the higher LAP may be transmitted to the RA during atrial filling, causing the right atrial A and V waves to be equal in amplitude. Changes in the components of atrial pressures may indicate pathologic ventricular function and cardiac rhythm. For example, a large V wave in the CVP may be caused by severe tricuspid regurgitation, which may reflect right heart failure, pulmonary hypertension, or right ventricular ischemia. Similarly, a large V wave in the LAP indicates mitral valve regurgitation. Disappearance of the A wave with appearance of an enlarged V wave indicates lack of atrial contraction because of loss of atrioventricular synchrony, as in junctional ectopic tachycardia, supraventricular tachycardia, atrial fibrillation, or atrial flutter (Figure 13.19). This is particularly important in discerning pathologic tachyarrhythmia from sinus tachycardia. In the face of rapid heart rate, the P wave of the ECG is often indiscernible, making cardiac rhythm from ECG difficult to determine. In contrast, the presence of an A wave in atrial pressure waveforms assures atrioventricular synchrony.

The transducer position is particularly important for accurate measurement of atrial pressure, and it is usually set at the level of the RA. Slight position changes can easily provide erroneously high or low numbers because both the CVP and LAP measure low pressures of several cmH_2O. Constant vigilance is necessary to keep the transducer level in the correct position and accurately calibrated.

KEY POINTS: INTERPRETATON OF INTRAVASCULAR PRESSURE WAVEFORMS

- Observation of the pressure waveform *per se* can provide additional diagnostic information and should be displayed continuously during pressure monitoring.
- Common errors made in data acquisition from arterial catheters include calibration error, improper calibration (gain), underdamping, and overdamping.
- In the presence of normal tricuspid and mitral valves, the CVP and LAP reflect their respective ventricular end-diastolic pressures.

Newer techniques in pediatric intravascular monitoring

Cardiac output monitoring

Because traditional percutaneous, balloon-tipped PA catheterization is limited in small children, and those with intracardiac shunting, several other recently derived methods invented for adults to measure CO and oxygen delivery in patients with CHD have been applied to infants and children [141]. Lithium dilution CO (LiDCO) uses a standard central line in the SVC or even a peripheral IV catheter, and a special femoral artery catheter equipped with a lithium-detecting electrode. A dilute solution of lithium chloride is injected into the vein, and arterial blood is withdrawn into



Figure 13.19 Electrocardiogram demonstrating normal sinus rhythm in the first third of the panel, with onset of supraventricular tachycardia. Note the arterial pressure tracing with a 12–15 Torr decrease in systolic pressure, and the loss of the A wave on the central venous pressure tracing, with the appearance of large V waves with a systolic pressure increase from 10 to 16 mmHg.

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the lithium electrode. The cardiac index is related to the AUC of the change of lithium concentration. This method has been demonstrated to have reasonable correlation with thermodilution CO in children after congenital heart surgery. In a study of 48 measurements in 17 patients weighing 2.6–34 kg, the correlation between LiDCO and thermodilution CO was good (r^2 = 0.96), and the mean bias was −0.1 ± 0.31 L/min [142].

Transpulmonary thermodilution CO uses a similar principle as LiDCO, except with temperature as the indicator instead of lithium concentration. Cold saline is injected into a CVC, and via a thermistor placed in a femoral artery, a time–temperature curve is derived, which correlates reasonably well with standard thermodilution CO as measured by a standard PA catheter [143]. Both lithium and any thermodilution method are limited to patients without any intracardiac shunting, significantly restricting their use in CHD.

Yet another newer method is pulse contour analysis of the arterial waveform (PiCCO,Pulsion Medical Systems, Gettinge AB, Feldkirche, Germany), which relates the contour and AUC of the systolic portion of the arterial waveform to the stroke volume, and thus the CO. This continuous method is periodically calibrated using the transpulmonary thermodilution CO as described above (again making the method invalid with intracardiac shunting) and demonstrates a good correlation with standard thermodilution with a PA catheter in a study of 24 pediatric patients after cardiac surgery (r^2 = 0.86, mean bias 0.05 ± 0.4 L/min/m^2) [144]. A standard central venous catheter is used for injection; and a special femoral arterial catheter, minimum size 3 Fr, are utilized with the PiCCO system (Figure 13.20 A-D). Stroke volume variation (SVV) and pulse pressure variation (PPV) can be calculated using the arterial waveform (see above), and fluid responsiveness can be assessed. SVV/PPV of 10% or less can be an indicator of adequate intravascular volume status. The PiCCO system will also derive a systemic vascular resistance index, stroke volume index, global end-diastolic index (a measure of preload), and contractility parameters. None of these parameters has published data pertaining to congenital heart disease patients. In 15 pediatric patients averaging 22.9 kg, with septic or cardiogenic shock without CHD, 49 cardiac index measurements by PiCCO had close correlation with echocardiographically derived cardiac index by the volume-time integral method (r = 0.94, $R2$ = 0.89, p < 0.01) [145] In this same patient cohort, global end-diastolic index derived with PiCCO had significant correlations with CVP, and echocardiographically-derived inferior vena cava collapsibility index in spontaneously ventilating patients, and the IVC distensibility index in mechanically ventilated patients. [146] There are no published pediatric outcome studies, and although a comprehensive review concludes that both lithium dilution and transpulmonary thermodilution methods have good correlation with standard thermodilution CO, these methods have not yet found their place in pediatric cardiac surgical care [147]. A 2018 survey of 97 pediatric cardiac intensivists from 62 international centers revealed that only 4% used PiCCO for diagnosis and to guide therapy in low cardiac output syndrome after cardiac surgery. [148]

Central venous oxygen saturation monitoring

Monitoring of intravascular oxyhemoglobin saturation using reflectance catheters has been used in the umbilical artery, PA, and adult-sized CVCs for a number of years, but only recently have standard pediatric sized 4 and 5 Fr, double- and triple-lumen CVCs become available for routine use to measure central venous oxygen saturation ($ScvO_2$) in pediatric patients. The advantage of this method is that it is a measure of oxygen delivery that is independent of intracardiac shunting, and thus may have better utility in the CHD patient. In 16 pediatric patients undergoing cardiac surgery, Liakopoulos et al. demonstrated good correlation between $ScvO_2$ as measured with the catheter and with blood co-oximetry (r^2 = 0.88, bias −0.03 ± 4.72%, precision −8.02 to +8.09%) [149]. Three more recent studies in 75 critically ill infants and children undergoing cardiac or other major surgery report a wider range of correlation (r^2 = 0.28 to 0.93), bias (−1.1 to +2.6%), and precision (−18 to +23%) [150–152]. Outcome data are lacking for this technique, but it has been useful as an adjunct for continuous trend monitoring of oxygen delivery in major cases.

Complications of vascular access

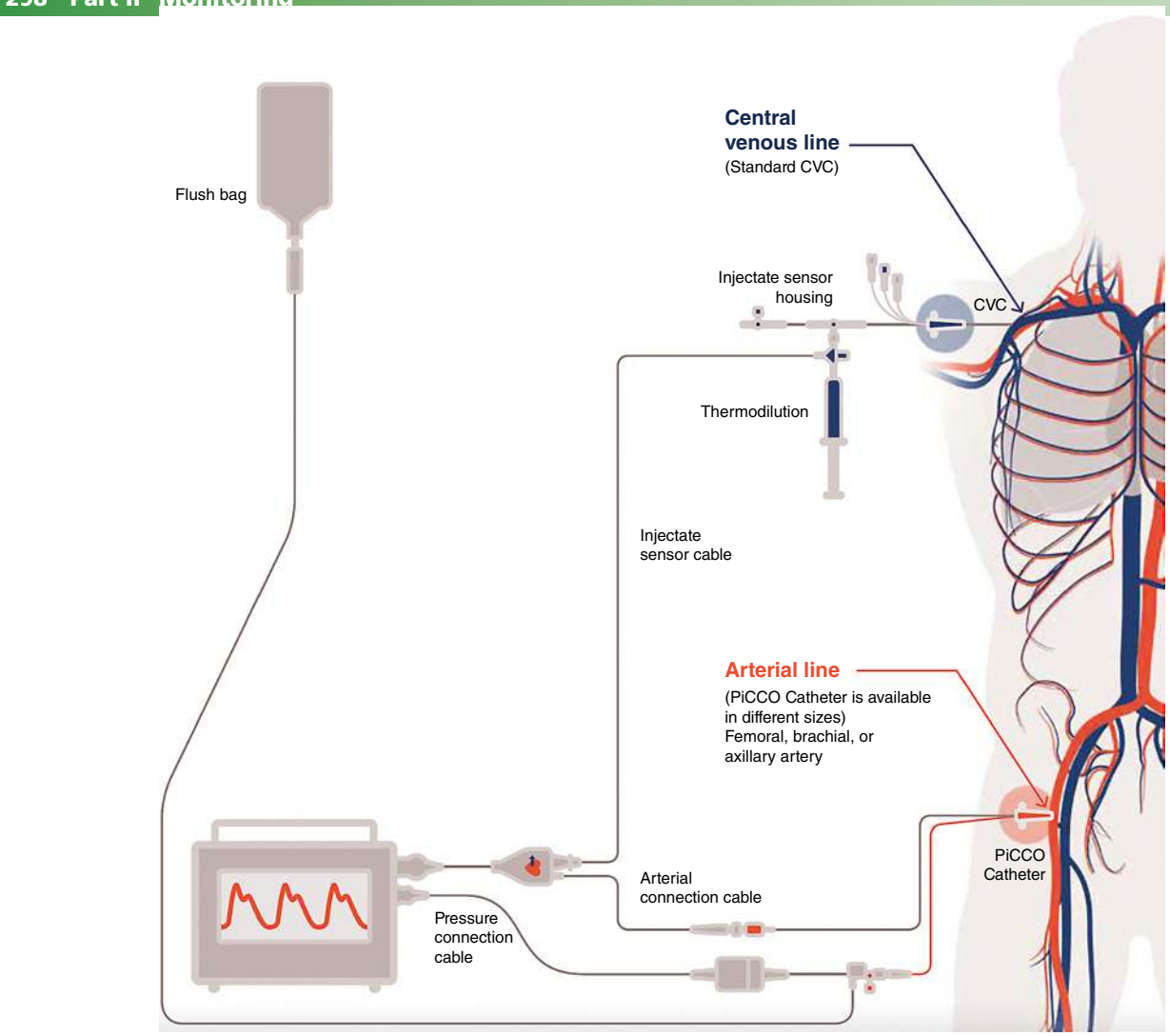
Incidence and risk factors

Central catheterization remains a mandatory procedure in many critically ill pediatric patients. Notwithstanding its certain advantages (e.g. large-bore catheters, monitoring, drug administration), central catheterization carries risks of serious complications. These can be categorized into mechanical or insertion-related complications (e.g. inadvertent arterial puncture, malposition, arterial catheterization, arrhythmia, hematoma, pneumothorax, hemothorax, cardiac tamponade) and maintenance-related complications (e.g. obstruction, occlusion, systemic venous air embolization, infection). If detected promptly, minor complications can be readily corrected; however, some (pneumothorax, hemothorax, cardiac tamponade) may be life-threatening. Sufficient knowledge and preparation, diligent technique, skill, and experience are obligatory.

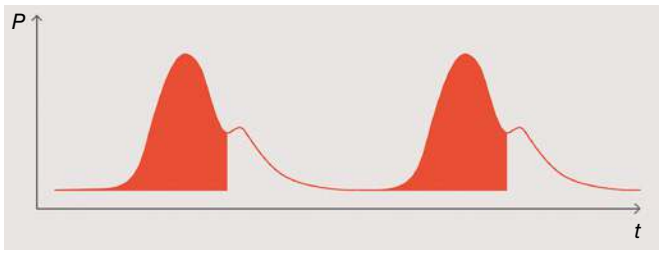
The incidence of all vascular access-related complications is difficult to ascertain from published research, but numerous case reports and studies have addressed this issue. Among early mechanical complications, the most frequent are arterial puncture, malposition, artery catheterization, and hematoma. The most frequent life-threatening complications are pneumothorax, cardiac tamponade, and hemothorax. The most frequent catheter maintenance-related complications are obstruction, occlusion, and sepsis.

The relationship between insertion site and complications has been well studied [153–155]. The SCV approach is anatomically more prone to early insertion-related complications [156] than IJV or FV catheterizations; however, significantly more maintenance-related problems develop in children with indwelling femoral catheters [155].

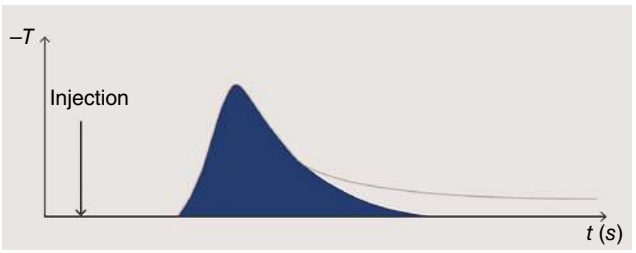
Operator experience appears to influence the rate of complications. In one study, resident anesthesiologists caused significantly more complications, both common and rare, than their senior colleagues; however, when closely



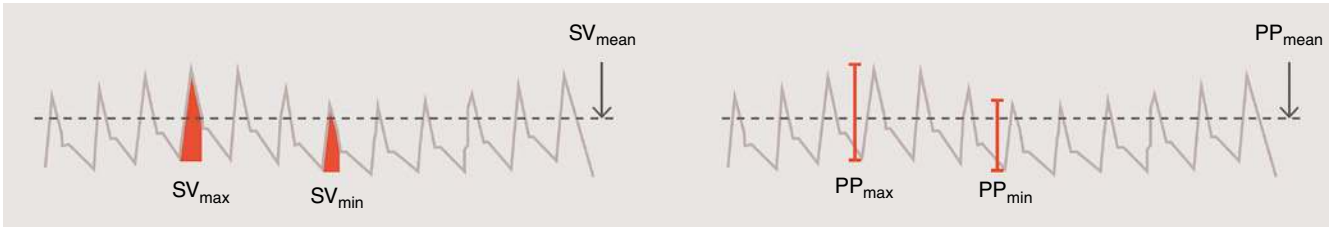
(A)



(B)



(C)



(D)

Figure 13.20 (A) Schematic of system: Cold saline is injected into a CVP port and transits the pulmonary circulation and is injected into the aorta; temperature change is measured by a sensitive thermistor in a specially designed femoral artery catheter. (B) Arterial waveform analysis: the area under the curve of the systolic portion of the arterial waveform (red shading) is calculated continuously, as a measure of stroke volume. (C) Transpulmonary thermodilution: The area under the curve correlates with cardiac output, much like standard thermodilution cardiac output with a thermistor in the pulmonary artery. (D) Stroke volume variation (SV) and pulse pressure variation (PP). Percent variation during inspiration and expiration around the mean values can be calculated as a measure of intravascular volume status. (Source: Figures courtesy of Pulsion Medical Systems, Gettinge AB, Feldkirche, Germany.)

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supervised, the rates of acute mechanical complications [90], deep vein thrombosis (DVT), and infection were lower. Lower complication rates and higher success rates were obtained after sufficient training in landmark and ultrasound-guided techniques [91].

In general, risk factors for central venous catheterization-related complications include previous unsuccessful insertion attempts, more than two punctures, inexperience, body mass index <20 and >30, previous catheterizations, previous catheterization attempts, previous operations, radiotherapy, severe dehydration or hypovolemia, and large catheter size [155]. In neonates, catheter insertion can be challenging due to anatomic difficulties [156]. In older children, insertion-related problems appear not to be associated with age; however, maintenance-related complications are more commonly observed in younger children [151]. Similar to the adult population, duration of catheterization is closely related to frequency of maintenance-related complications in pediatric patients [155].

Totally implantable central catheters (ports), PICCs, and tunneled external central catheters (e.g., Broviac catheters) have been used more often in critically or chronically ill pediatric patients. In a study summarizing implanted catheter-related issues, the overall rate of reported complications was 31%; leakage was a specific problem necessitating reinsertion or repair. Infections were observed in 6% of patients with implanted central catheters and developed more than 30 days after catheterization [157]. When Broviac and clampless valved catheters were compared, malfunction was more frequently observed in the former group, whereas catheter displacement was more commonly found in the latter [158].

Thrombosis

Catheter thrombotic occlusions and catheter-related thrombosis in pediatric patients have become increasingly prevalent. The incidence of central catheter-related DVT has been reported to be 0.13/1,000 catheter-days [159]. This is one of the most frequent complications, especially among infants. Central venous thrombosis is reported to occur in 5.8% of neonatal patients, 10 times that of older patients; 40–50% of central venous thrombosis in this group occurs after congenital heart surgery [160]. A recent study examining the incidence of asymptomatic CVC-related DVT in pediatric ICU patients revealed that age was independently associated with DVT; children aged more than 13 years were more likely to develop DVT than those aged less than 1 year [161].

Factors contributing to the risk of thrombosis include large-bore catheters in small vessels (i.e., larger than 4 Fr in small infants), duration of cannulation exceeding 7 days, venous stasis due to extreme fluid restriction or low CO, infusion of high-osmolarity fluids, and hypercoagulable states.

Indwelling central catheters act as additional foci for clot formation, and migrating clots can obstruct pulmonary, coronary, and cerebral vessels, leading to life-threatening events. Rare conditions, such as arteriovenous malformations, may serve as sources of emboli; the brain is at particular risk of paradoxical embolism, further facilitated by the presence of right-to-left intracardiac shunts and pulmonary vascular abnormalities [162].

Immediate consequences of SVC thrombosis include SVC syndrome [12] with increased intracranial pressure and chylothorax due to ineffective drainage of the thoracic duct. Thrombosis of the IVC results in renal and intestinal dysfunction, ascites, and edema of the lower abdomen and extremities [153]. Assess carefully for signs of thrombosis; suspicion of thrombosis should be evaluated by ultrasound examination [163].

A wide range of options is available for the management of catheter-related thromboembolism. These include removing the catheter, heparinization, administration of thrombolytic agents such as tissue plasminogen activator and urokinase, antithrombin III replacement, and surgical thrombectomy. In children, 5,000 IU of intraluminal urokinase was reported to be as effective as 25,000 IU in resolving withdrawal occlusion in partially implanted central catheters [164]. Systemic urokinase may rescue a significant proportion of central catheters refractory to intraluminal urokinase or those apparently completely occluded.

Prevention of SVC thrombosis is crucial and avoiding SVC catheterization in patients weighing less than 4 kg is often preferable. In children undergoing superior cavopulmonary anastomosis, EJV catheterization reliably predicts IJV and pulmonary arterial pressures and may obviate the risk of life-threatening cavopulmonary thrombosis [39]. Thrombosis is also associated with higher rates of infection [165, 166]. Heparin-bonded catheters can decrease the rate of thrombosis and do not increase the risk of bleeding [165, 167]. In patients with occlusion of central veins due to previous catheters, magnetic resonance venography can be useful in identifying patent veins for future interventions [168].

Thrombosis or dissection of an artery is a serious complication that must be treated immediately.[169, 170] It is important to inspect the distal extremity after catheter placement, comparing it with the contralateral extremity, assessing capillary refill, and to palpate distal pulses. Place a pulse oximetry probe distal to the catheter to serve as a continuous monitor for potential vascular insufficiency. Transient compromise of perfusion immediately after placement of a catheter, due to arterial spasm or during low output states, may be observed. If perfusion of an extremity is significantly compromised, ultrasound examination, removal of the catheter, use of vasodilators, warming the extremity, administration of heparin or thrombolytics, surgical consultation, thrombectomy, or surgical reconstruction is indicated. Microsurgical repair with a saphenous vein graft rather than simple thrombectomy is preferred by some groups for repair of small arteries with dissection or other significant injury. [171, 172]

Neonatal arterial thrombosis has become more common with the use of umbilical artery catheters [173]; however, catheter-induced aortic thrombosis is rare. In a study of approximately 4,000 infants with an inserted umbilical artery catheter, 44 developed major thromboembolic problems requiring varying degrees of surgical management [174]. The most common location of arterial thrombosis associated with umbilical artery catheterization in neonates is the abdominal aorta [173].

It is possible to use ultrasound to measure the diameter of arteries before cannulation; generally, the largest diameter artery is preferable. Previous cardiac catheterization is often

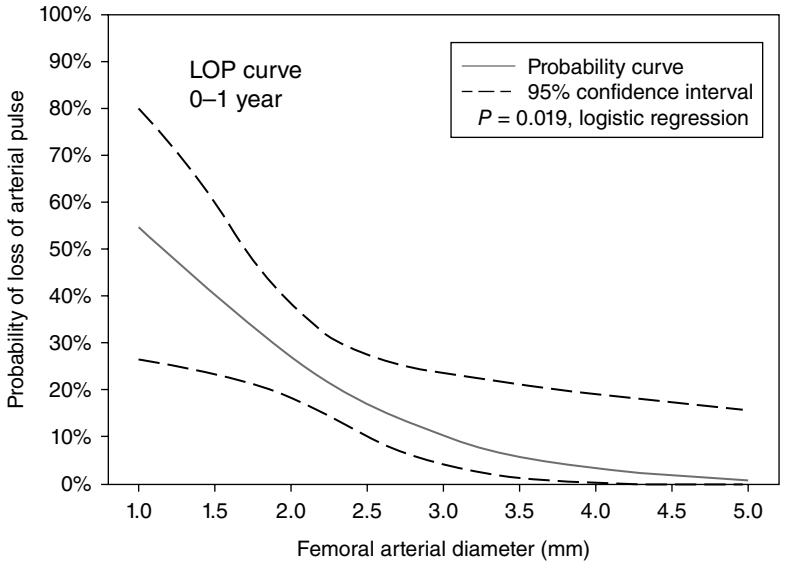


Figure 13.21 Probability curve for loss of palpable pedal pulse (LOP) at the end of the cardiac catherization procedure in which the femoral artery was accessed in children between the age of 0–1 year. A significant increase occurred with artery diameter less than 3 mm. (Source: Tadphale et al. [174]. Reproduced with permission from Springer Nature.)

via the right femoral artery, potentially reducing its diameter. In the case of the femoral artery, puncture of the common femoral artery above the bifurcation into superficial and profunda femoris arteries is preferable because of the larger diameter at that level. The smallest catheter size (see above) should be utilized to minimize the risk of thrombosis. In a prospective study of 400 cardiac catheterization patients aged 0–4 years, a femoral artery diameter of less than 3 mm was associated with a significantly increased risk of loss of pedal pulses after the procedure [174] (Figure 13.21). NEW Similarly, ultrasound examination of the diameter of femoral veins pre-cannulation can be effective at choosing the larger vessel and increasing cannulation success and decreasing risk of thrombosis.

In a report by Kamyscek and colleagues of institution of routine postcatheterization ultrasound within 4 hours, in the 349 patients less than 6 months of age, incidence of detection of femoral arterial thrombosis increased from 8.3 to 23.4% with routine ultrasound.($p = 0.006$) Risk factors included lower weight, larger arterial sheath size, and longer procedure duration. Treatment was with unfractionated, or low molecular weight heparin and was successful in all cases. This data suggests that clinical signs and symptoms of femoral artery thrombosis are less sensitive than ultrasound due to collateral flow; and that high index of suspicion for arterial thrombosis in small patients should trigger early formal ultrasound examination to facilitate successful non-invasive therapy. [175]

Infection

Catheter-related sepsis can result in significant morbidity, increased mortality, prolonged ICU stay, and increased expense. Numerous studies have described the incidence of, risk factors for, and management of catheter-related infections. Sepsis was reported in 5.8–7.6% of pediatric patients, and the rate of catheter-related bloodstream infections (CRBSIs) was 0.1–6.4 infections/1,000 catheter-days [44, 176, 177]. The incidence of arterial catheterization-related infections in the pediatric population is very low; the calculated rate is 6.2% [178]. The pathogen mainly responsible is *Staphylococcus epidermidis*, and its colonization is not dependent on the catheter insertion site [155].

Risk factors for CRBSIs include weight less than 8 kg, cardiac failure, cancer, silicone catheters, guidewire exchange catheterization, obstructed catheters, and more than 12 days of catheter placement [179]. A higher incidence of central line-associated bloodstream infections was found in children between 1 and 2 years of age [180]. The safe period for an indwelling CVC is 3 days in infants less than 12 months old and 6 days in older children; the infection rate increases if catheters are left in place for more than 10 days [180]. The number of catheter lumens does not appear to influence the rate of this complication [44].

Several strategies may be used to reduce catheter-related infections [181]. First is the use of full barrier precautions (e.g., sterile gown, mask, gloves, and careful aseptic technique during insertion). Second, a potent antiseptic solution should be used for skin scrubbing and during redressing of the insertion site every 3–7 days. In addition, systemic antibiotic administration or antibiotic bonding to the resin of the catheter may be advantageous (Box 13.1).

Chlorhexidine has been shown to be superior to other antiseptic solutions and is being used more frequently for catheter insertion-related antisepsis. Novel chlorhexidine-impregnated dressings or chlorhexidine-impregnated sponges are safe and effective in preventing CRBSIs and non-catheter-related bloodstream infections in neonates requiring prolonged central venous access, and their use significantly reduces the rates of central catheter colonization in infants and children after cardiac surgery [182–184]. Although it provides effective skin protection, chlorhexidine may cause contact dermatitis, particularly in low-weight infants, and some cases of

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Box 13.1: Central line catheter care bundles

Insertion bundle
- Use full sterile barrier precautions: gown, cap, mask, gloves, wide sterile draping
- Wash hands before the procedure
- For all children aged ≥2 months, use chlorhexidine gluconate to scrub the insertion site for 30 seconds for all areas except the groin, which should be scrubbed for 2 minutes. Scrubbing should be followed by 30–60 seconds of air drying
- No iodine skin prep or ointment is used at the insertion site
- Use a sterilized prepackaged tray with catheter that contains all necessary equipment and supplies including full sterile barriers
- Create an insertion checklist, which empowers staff to stop a non-emergent procedure if it does not follow sterile insertion practices
- Use only polyurethane or Teflon catheters[a]
- Conduct insertion training for all care providers, including sides and video

Maintenance bundle
- Assess daily whether catheter is needed
- Catheter-site care
  - No iodine ointment
  - Use a chlorhexidine gluconate scrub to sites for dressing changes (30 seconds scrub, 30 seconds air-dry)
  - Change gauze dressings every 2 days unless they are soiled, dampened, or loosened[a]
  - Change clear dressings every 7 days unless they are soiled, dampened, or loosened[a]
  - Use a prepackaged dressing-change kit or supply area
- Catheter hub, cap, and tubing care
  - Replace administration sets, including add-on devices, no more frequently than every 72 hours unless they are soiled or suspected to be infected
  - Replace tubing that is used to administer blood, blood products, or lipids within 24 hours of initiating infusion[a]
  - Change caps no more often then 72 hours (or according to manufacturer recommendations); however, caps should be replaced when the administration set is changed[a]
  - The prepackaged cap-change kit, or supply area elements to be designated by the local institution

[a] These procedures are according to the Centers for Disease Control and Prevention recommendations.

anaphylactic reaction to chlorhexidine-impregnated catheters have also been reported [185].

The use of antibiotics for prevention of central catheterization-related infections has not yet been supported by strong evidence. Although vancomycin added to the solution used for total parenteral nutrition effectively reduced catheter-related sepsis in a neonatal ICU and offered potential benefits (e.g. fewer catheters, earlier weight gain), its widespread implementation has not been recommended [186]. The addition of vancomycin to heparin flush solutions did not reduce bacteremia with vancomycin-susceptible organisms [187]. In a meta-analysis of 21 randomized controlled trials comparing the incidence of specific bacterial and fungal species colonization on minocycline/rifampicin-impregnated catheters, the proportion of all colonized antibiotic-impregnated catheters found to harbor *Candida* species was greater than the proportion of all colonized non-impregnated standard catheters [188]. Commercially available antimicrobial catheters may become colonized with distinct microbial flora, probably related their antimicrobial spectrum of activity [188].

Suspected CRBSI should be addressed by peripheral blood culture and blood culture from the central catheter. Remove the catheter when possible and send the tip for bacterial culture. Design antibiotic therapy empirically against the most common institution-specific pathogens and provide coverage for *S. epidermidis*. Proper education may also reduce infection frequency; in a quasi-experimental study designed to improve the quality of clinical practice in a neonatal ICU, the rate of CRBSIs decreased from 8.4 to 1.28 cases/1,000 central line-days [189].

Malposition/perforation

Perforation of a vein or the heart can occur during CVC placement or any time thereafter. The cause of perforation can be a needle, guidewire, dilator, or the catheter itself. Malpositioning of the CVC may not necessarily lead to complications *perse*, but a catheter tip in the RA [190, 191] or not parallel to the SVC clearly predisposes to subsequent complications. Other predisposing factors for CVC perforation include a left-sided approach, use of a guidewire end without a flexible tip, a stiffer catheter, and "long-arm" CVC inserted in the basilic or cephalic veins. With left-sided lines, the catheter tip is frequently at a 45°–90° angle to the SVC or atrium. Models have shown that this position is more likely to lead to great vessel perforation [192]. Up to 5–10% of patients with CHD have a left SVC [193], which drains most often into the coronary sinus or left atrium; both of these sites are undesirable for catheterization. An ideal position is in the mid-SVC, with the tip parallel to the vein wall. Long-arm CVCs tend to be more mobile than other CVCs, thus increasing the possibility of the catheter tip migrating into the RA with arm movement. The material of which catheters are made may also be associated with incidence of this complication; soft polyurethane or silicone catheters are much less likely to perforate than stiffer polyethylene catheters [194].

Inability to consistently aspirate blood, abnormal waveform, or signs or symptoms of pericardial tamponade or hemothorax indicate perforation. Treatment involves aspiration of as much blood as possible through the catheter and establishment of alternate access; intravascular volume replacement; and drainage of the pericardial or pleural blood by needle or surgical exploration. Confirmation of catheter tip location with an anteroposterior radiograph after insertion is obligatory.

The mid-SVC, above the pericardial reflection, is the recommended position for the catheter tip; however, positioning a multi-lumen catheter too cephalad in the SVC may result in a situation in which one of the proximal ports is not inside the jugular vein, leading to extravascular extravasation of important or caustic drugs or fluids. Many studies of catheter placement in children have shown that the internal jugular route results in tip placement in the SVC or RA 98–100% of the time, whereas the subclavian route results in a 5–15% rate of catheter malposition (i.e., across the midline in the contralateral brachiocephalic vein or up the ipsilateral IJV).

Accurate CVP measurements are generally obtained with IVC catheters, whether placed above or below the diaphragm. Umbilical venous catheters should be placed above the diaphragm at the IVC–RA junction, but not in the RA, to ensure passage through the ductus venosus and a parallel position to the IVC wall [195].

Some rare, inadvertent, CVC placement locations have been reported. Catheters may pass into the superior intercostal, thymic, azygos, or ascending lumbar veins or even into the liver parenchyma, depending on the insertion site [196–198]. Dural puncture, intrathecal catheterization, or extradural catheter insertion have also been reported [199–202]. In a case report, neurologic complications (paraplegia, urine retention, and milky cerebrospinal fluid) developed after abnormal placement of a catheter into the lumbar venous plexus via the left saphenous vein [198]. If malposition is strongly suspected, the catheter must be removed, and the patient assessed for other complications.

Pneumothorax/hemothorax

Pneumothorax occurs in 7% of central venous catheterization cases [203], being most frequent with the subclavian approach (2.6%) [204], but it may also occur with the IJV approach (0.38%) [87], especially with low puncture sites. In four reported cases of hemothorax [205–208], the complication resulted in a fatal outcome in all cases. Perforation of the punctured vein, leading to pneumo- or hemothorax, may be caused not only by the advancing needle (as in the Seldinger technique), but also by guidewires, dilators, or relatively rigid catheters.

Pneumothorax and hemothorax can be avoided by cautious advancement of needles, guidewires, dilators, and catheters. An ultrasound guidance system greatly facilitates catheter insertion when used properly. The following tips may also be helpful:

- In the subclavian approach, it is important to advance the needle only during expiration.
- A very shallow approach, with the needle directed just posterior to the clavicle and at the sternal notch, is recommended.
- For the IJV, a higher puncture site and limit of caudad advancement of the needle to stop above the clavicle are preferable.
- Continuous aspiration with a saline-filled syringe should be performed as the needle is advanced.
- If air is aspirated, stop puncture attempts immediately and monitor carefully for compromise of ventilation and hemodynamics. Chest radiography should be performed, and pleural drainage should be initiated if indicated. After sternotomy, the pleura can be opened on the side where the pneumothorax is suspected or diagnosed.

Cardiac tamponade

Cardiac tamponade is a severe complication of central venous catheterization and is closely related to catheter malposition and vessel perforation during puncture or placement. The incidence of cardiac tamponade after pediatric cardiac surgery ranges from 0.04 to 7% [209]. Catheter characteristics (rigid polyethylene catheters are more likely to cause tamponade than flexible silicone or polyurethane catheters [192]) and vessel wall tear caused by an abnormally placed catheter might be associated with increased risk of tamponade, but detailed studies have not been carried out. Age-associated difficulties with catheter insertion may also be related to a higher risk. In a study of 10 children with cardiac tamponade, 7 were infants, and most complications occurred during needle advancement, with symptoms developing within minutes to up to 12 hours after the procedure [210].

Inadvertent arterial puncture or catheter placement

Inadvertent puncture of the CCA during IJV catheterization is a well-recognized complication; however, other arteries, including the subclavian, vertebral, transverse cervical, and thyroid inferior arteries, are occasionally located behind the IJV and are at risk of perforation [208, 211, 212]. Some authors suggest identifying the presence of vertebral arteries to avoid accidental puncture during IJV catheterization in pediatric patients [96, 98].

Inadvertent arterial puncture can nearly always be prevented by the use of ultrasound guidance. The presence of potential anatomic variations should be confirmed with ultrasound Doppler color flow imaging, and real-time, ultrasound-guided venipuncture should follow a preprocedural ultrasonographic assessment [96, 98].

If this complication occurs, the following principles may be useful. After needle puncture, remove the needle immediately, elevate the area, and hold firm pressure for 5–10 minutes. A small-bore needle puncture of the carotid or femoral artery (e.g., 20 ga or smaller) is not usually an indication to cancel surgery. If a larger hole is created (i.e., a dilator and catheter have been placed), pressure transduction can be used to confirm the location. In this case, a discussion with the surgeon must ensue. Normally, the catheter can be removed, and pressure held without consequences, unless a very large catheter was used (e.g., introducer sheath or large-bore CVP catheter), in which cases surgical exploration and repair should be undertaken. In most cases of elective cardiac surgery, it is prudent to postpone the surgery if a large hole has been made in the artery. Surgery can usually be performed safely 24 hours later, if no bleeding has occurred. If surgery must proceed after an unintended arterial puncture with a large needle or catheter, sterile preparation of the site and inclusion in the surgical field are prudent to facilitate direct observation and access for repair during the surgery if indicated.

Arrhythmias

Central catheters and guidewires can cause arrhythmias. Too deep advancement of the catheter or guidewire has been associated with ectopic atrial tachycardia, especially with the catheter tip in the RA mechanically stimulating and potentially injuring the conduction system of the heart. Atrial fibrillation is also associated with CVC placement. Arrhythmias occur more commonly with passage of the guidewire. These include isolated PACs, supraventricular tachycardia, and, if the guidewire is advanced into the RV,

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premature ventricular contractions or even ventricular tachycardia or fibrillation.

For prevention, a marked guidewire should be used for IJV catheterization. Extreme care must be taken when passing a guidewire to stop advancement if significant arrhythmias are encountered, and when advancing the catheter over the wire. Guidewires must be advanced at as shallow an angle as possible, and in accordance with the body size of the patient. Pediatric patients at particular risk of arrhythmia are those with a known history of arrhythmia, cardiomyopathy, or RV hypertrophy [213]. Cardioversion is effective when atrial fibrillation or life-threatening supraventricular tachycardia develops [213, 214].

Systemic venous air embolus

Systemic air embolus is a constant threat for patients with central or peripheral venous catheters and intracardiac shunting, particularly those with two ventricles and right-to-left shunting and infants with a single ventricle and obligate mixing of systemic and pulmonary venous return in the systemic ventricle. Air may lodge in the coronary arteries, especially the right, the PA, or the brain, leading to potentially serious consequences. The incidence of venous air embolization caused by central or peripheral IV catheters has not been studied in detail, and it is possible that this complication is vastly underestimated or even neglected [215].

Large air emboli can be observed by TEE or transcranial Doppler ultrasound, but prevention is most important. Extreme attention must be paid to avoid the introduction of air into the systemic venous circulation. Careful preparation of venous infusions includes the following: thorough de-airing of all infusions before connection; de-airing of continuous-flush central venous lines; air filters on continuous infusions; and careful technique when injecting drugs and fluids, which involves holding the syringe upright, flushing fluid from the proximal IV tubing, and aspirating and tapping the syringe before injection [216]. Constant vigilance, the use of TEE to monitor for intracardiac air and transcranial Doppler for systemic arterial air, and meticulous technique of catheter removal may reduce the risk of air embolus.

Foreign bodies

Embolization of catheter or guidewire fragments sheared off during difficult insertion procedures, and disrupted catheter fragments in response to repeated mechanical compression between the clavicle and the ipsilateral first rib have been reported [217, 218]. The latter, known as "pinch-off" syndrome, develops occasionally after a long period of catheter indwelling (1 month to 3 years) and poses many treatment difficulties [218]. Prevention includes selection of alternative techniques (percutaneous supraclavicular or IJV approaches or ultrasound-guided catheterization of the axillary vein). If resistance is encountered when withdrawing the guidewire, the guidewire and the needle, or the catheter and the needle, must be withdrawn completely from the vessel together as a unit. Before insertion of long-term indwelling catheters (e.g., for home parenteral nutrition), information should be provided to patients and/or their caregivers regarding possible complications related to catheter shearing.

Complications related to intracardiac catheters

This category is unique to children undergoing congenital heart surgery because intracardiac catheters are rarely used in other situations. In a large retrospective study of 6,690 transthoracic intracardiac catheters in 5,666 pediatric cardiac patients over a 10 year period, there was an overall 0.6% incidence of serious complications, defined as significant bleeding or catheter retention [49]. The risk was greatest for PA catheters (1.1%, with three cases of severe cardiac tamponade and one death for 1,680 catheters) followed by left atrial catheters, then right atrial catheters. The authors concluded that the benefits of intracardiac catheters far outweigh associated risks if care is exercised in placing and removing them and if complications are recognized rapidly and managed aggressively. However, another study reported a relatively high complication rate (37%) of bleeding in 523 transthoracic intracardiac catheters (276 right atrial, 155 left atrial, 68 common atrial, and 24 RV or PA catheters), with the highest rate (47%) in left atrial catheters [219]. These bleeding events required intervention in 8.3% of the patients and caused hemodynamic compromise in 2.6%.

More recent single center studies report similar intracardiac catheter complication rates. Stein and colleagues reported 176 transthoracic catheters in 124 neonates, of which 37% were right atrium, 27% common atrium, and 34% left atrium, with only one PA catheter. 20% of patients received packed red blood cell transfusions after line removal, but there were no deaths, cardiac arrests, or ECMO cannulations [220]. Beham and colleagues reported 115 intracardiac catheters in 112 patients; 45 were RA, 68 LA, and 2 PA catheters [221].

Serious complications occurred in 5.1% of patients, with bleeding requiring transfusion in 3.5%, cardiac tamponade resulting in death in one patient, and tension pneumothorax in one patient. These outcome studies suggest that PA catheters are associated with the highest risk of adverse events; they are used less frequently in more recent reports. Although intracardiac lines are a common vascular access modality with low risk of serious adverse events, a well-established protocol for their removal, with corrected coagulation, mediastinal drainage tube in place, adequate patient sedation, packed red blood cells available, and emergency response surgical team available, is important to minimize adverse outcomes. To date, there have been no outcome studies available comparing transthoracic and percutaneous catheters.

Other complications

Chylothorax [222], phrenic nerve injury [223, 224], vertebral arteriovenous fistula [225], brachial arteriovenous fistula [226], Horner's syndrome [227–229], and tracheal puncture [230] have also been described. These complications can be prevented by skilled personnel and the use of ultrasound-guided techniques to accurately identify vessel location.

KEY POINTS: COMPLICATIONS OF VASCULAR ACCESS

- Complications associated with vascular access can be categorized into catheter insertion- and maintenance-related complications. The most common are arterial puncture and catheter obstruction, respectively.
- The most frequent life-threatening complication of central catheterization is pneumothorax.
- Insertion-related complications occur more frequently with the subclavian approach than with the IJV or femoral approach.
- Appropriate training in pediatric central catheterization, especially in ultrasound-guided techniques, can reduce complications.
- To avoid serious or life-threatening outcomes, risk factors for central catheterization-related complications in children and those for central catheterization-related bloodstream infections should be taken into consideration when planning the procedure.

Conclusions

Vascular access in children undergoing surgery for CHD can be challenging and presents a difficult task for pediatric anesthesiologists. Each needs to gain experience and proper technique to develop his or her own approach to vascular access. No one approach has been shown to be superior to another. However, there is accumulating data favoring ultrasound-guided catheter insertion and we believe this technique will become a standard practice for percutaneous central venous access because the importance of decreased complication rates, insertion time, and expense cannot be overemphasized. Attention to the details of vascular access is important for enhancing patient safety. This, along with a strategy to preserve access sites in small infants with single-ventricle physiology and who may need multiple cardiac surgeries, ultrasound-guided line placement and the use of antibiotic-impregnated catheters will improve the outcome of vascular access procedures.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Yen K, Riegert A, Gorelick MH. Derivation of the DIVA score: a clinical prediction rule for the identification of children with difficult intravenous access. Pediatr Emerg Care 2008;24:143–7. The DIVA score uses four variables: history of prematurity, patient age, vein palpability, and vein visibility, and may predict failed first IV attempt in pediatric patients.

17 Andropoulos DB, Stayer SA, Bent ST, et al. A controlled study of transesophageal echocardiography to guide central venous catheter placement in congenital heart surgery patients. Anesth Analg 1999;89:65–70. In the cardiac OR setting, TEE-guided central venous catheterization results in 100% correct placement in pediatric patients.

65 Shindler E, Kowald B, Suess H, et al. Catheterization of the radial or brachial artery in neonates and infants. Pediatr Anaesth 2005;15:677–82. Using a relatively large retrospective dataset, this study demonstrates safety profiles of brachial artery catheterization using small catheters (24 or 22 ga) in neonates and small children.

79 Lamperti M, Bodenham AR, Pittiruti M, et al. International evidence-based recommendations on ultrasound-guided vascular access. Intensive Care Med 2012;38:1105–17. This article provides a condensed version of the formal recommendations by acknowledged experts on ultrasound guidance during vascular access in both adults and children.

80 Chuan WX, Wei W, Yu L. A randomized-controlled study of ultrasound prelocation vs anatomical landmark-guided cannulation of the internal jugular vein in infants and children. Paediatr Anaesth 2005;1:733–8. A two-dimensional ultrasound prelocation technique using an intraoperative transesophageal echocardiography probe can increase cannulation success rate and reduce the incidence of complications of central venous catheterization in infants and children.

81 Hosokawa K, Shime N, Kato Y, et al. A randomized trial of ultrasound image-based skin surface marking versus real-time ultrasound-guided internal jugular vein catheterization in infants. Anesthesiology 2007;107:720–4. An ultrasound-guided skin-marking method can enhance procedural efficacy and safety of internal jugular catheterization in neonates and infants.

82 Byon HJ, Lee GW, Lee JH, et al. Comparison between ultrasound-guided supraclavicular and infraclavicular approaches for subclavian venous catheterization in children – a randomized trial. Br J Anaesth 2013;111:788–92. The supraclavicular approach during SCV catheterization under ultrasound guidance can yield a shorter puncture time and decrease the incidence of guidewire misplacement compared with the infraclavicular approach in pediatric patients.

91 Malbezin S, Gauss T, Smith I, et al. A review of 5434 percutaneous pediatric central venous catheters inserted by anesthesiologists. Pediatr Anesth 2013;23:974–9. A prospectively collected large dataset that revealed a very high success rate for CVC via the IJV (99.5%) and a low immediate complication rate (1.3%) when inserted by trained anesthesiologists using the landmark technique.

108 Ishii S, Shime N, Shibasaki M, et al. Ultrasound-guided radial artery catheterization in infants and small children. Pediatr Crit Care Med 2013;14:471–3. In infants and small children undergoing congenital cardiac surgery, ultrasound-guided radial artery cannulation increases success rate, shortens the time for successful placement, and reduces complication rates compared with the traditional palpation method.

112 Song IK, Choi JY, Lee JH, et al. Short-axis/out-of-plane or long-axis/in-plane ultrasound-guided arterial cannulation in children: a randomised controlled trial. Eur J Anaesthesiol 2016;33:522–7. A controlled study of short axis vs. long axis ultrasound imaging for radial artery catheterization in 97 infants and children revealed no difference in success rate (94% short axis vs. 98% long axis), time to cannualtion, or complications. The incidence of puncturing the posterial arterial wall was higher in the short axis group; (96 vs. 18%, $p < 0.001$).

182 O'Grady NP, Alexander M, Dellinger EP, et al. Healthcare infection control practices advisory committee. Guidelines for the prevention of intravascular catheter-related infections. Infect Control Hosp Epidemiol 2002;23:759–69. These guidelines provide evidence-based recommendations for preventing catheter-related infections, emphasizing education and training, maximal sterile barrier precautions, skin antisepsis, and antibiotic-impregnated CVC.

CHAPTER 14
Neurological Monitoring and Outcome

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Introduction

Operative management of the child with congenital heart disease (CHD) was largely refined to its current state in the decades prior to the year 2000, during which operative mortality improved substantially. Data from the metropolitan Atlanta congenital defects program showed a profound increase in 1-year survival of the most critical heart defects, including hypoplastic left heart syndrome (HLHS), truncus arteriosus, pulmonary atresia, tricuspid atresia, and Tetralogy of Fallot from 67% (1979–1993) to 83% (1994–2005) [1]. Predictably, the increased expectation of survival is accompanied by willingness to perform surgery on increasingly complex patients. A multi-institution comparison of survival rates by case complexity using the Risk Adjustment for Congenital Heart Surgery (RACHS) showed a shift of fewer RACHS category 1 cases (low complexity) and more RACHS category 3, 4, and 6 cases (higher complexity) between 1996 and 2004. Further, mortality of RACHS category 6 (predominantly Norwood stage I palliation for HLHS) cases decreased from 48% in 1996 to 17% in 2004 [2]. The most common neonatal operations in the Society of Thoracic Surgeons' Congenital Heart Surgery Database are Norwood stage 1 palliation at 10.2% and arterial switch operation without ventricular septal defect (VSD) at 6.9%, and the surgical mortality of these lesions has decreased to 13.8%, and 2.0%, respectively, as of 2019 [3].

Despite these remarkable gains, survivors of complex CHD are at risk of having a characteristic array of neurodevelopmental deficits. These include poor impulse control, attention deficit/hyperactivity, mild language and cognitive deficits, and limited executive functioning ability [4–8]. Often appearing outwardly normal, children with such deficits perform poorly in academics and lack employability; they suffer high rates of depression and poor quality of life [9–14]. In addition to potentially modifiable factors, the presence of genetic syndromes and increasing complexity of the cardiac lesion are associated with a higher incidence of neurodevelopmental disability (Figure 14.1) [15]. The relative role of modifiable (acute neurologic injuries) and nonmodifiable factors contributing to the neurologic abnormalities seen in patients with CHD is a subject of study and debate. This chapter, written for the anesthesiologist, has an understandable bias toward discussion of the potentially modifiable perioperative factors that have been associated with neurologic injury. The pediatric cardiac anesthesiologist should be familiar with acute, perioperatively acquired neurologic injuries in this population and proposed strategies to avoid them.

Acute neurologic injury in the perioperative period has been quantified using magnetic resonance imaging (MRI)

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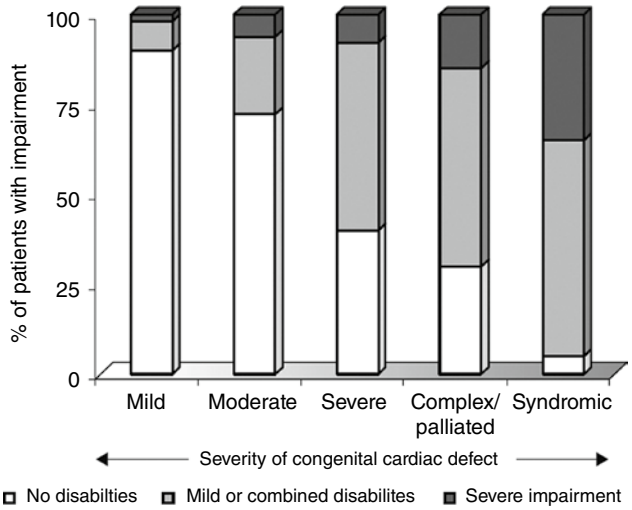


Figure 14.1 Schematic presentation of neurodevelopmental abnormalities in children with congenital heart disease (CHD). Children with milder forms of CHD (e.g., ventricular septal defect without an associated genetic syndrome) have a low incidence, and more than mild abnormalities are rare. Increasingly complex forms of CHD (e.g., transposition or total anomalous pulmonary venous connection) are associated with increasing risk of neurodevelopmental deficits. Only the minority of children with very complex CHD (e.g., functionally univentricular heart, hypoplastic left heart syndrome) are completely normal in all respects. CHD associated with chromosomal abnormalities (e.g., Down's and DiGeorge syndromes) or multiple congenital anomalies (VACTERL, CHARGE associations) are nearly always associated with neurodevelopmental abnormalities, in many cases severe. (Source: Wernovsky [15]. Reproduced with permission from Cambridge University Press.)

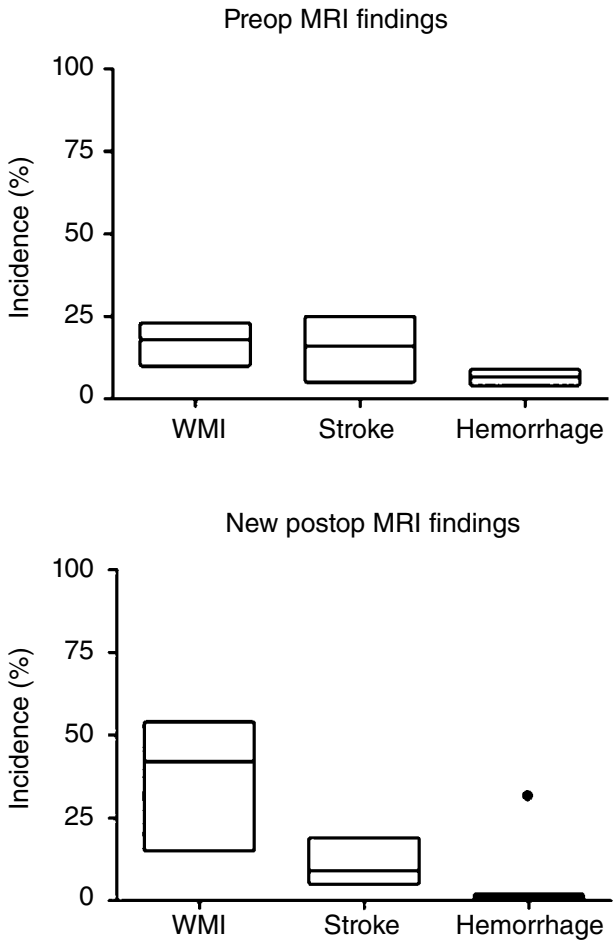


Figure 14.2 The incidence of preexisting and new postoperative neurologic injuries diagnosed by brain magnetic resonance imaging (MRI) observed in neonates subjected to cardiopulmonary bypass. The findings are compiled from six reports, seven centers, and 400 subjects. Median and range are shown with on outlier. WMI, white matter injury. Data are from references [16–23].

technology. Preoperative neurologic injuries visible by MRI occur with an incidence between 20 and 40% in newborns with critical heart defects [8, 16–18]. After surgery, 35–75% of patients will have a new lesion [19]. Despite differences in nomenclature of MRI findings, it is clear that the preponderance of *new* injuries seen after cardiac surgery in the infant occurs in the white matter (see Figure 14.2) [16, 17, 19–23]. Most studies further specified the preponderant white matter lesion as periventricular leukomalacia, an injury that has been extensively described in preterm infants exposed to extrauterine life (see Figure 14.3). In the preterm population, periventricular leukomalacia is associated with reduction in brain growth and neurodevelopmental impairments with deficits similar to those described in children with critical heart lesions [24, 25]. Current understanding of the pathogenesis of preterm periventricular leukomalacia posits that the preterm brain is susceptible to ischemia due to an incomplete redundancy of penetrating arterioles in the deep white matter, combined with a population of developing oligodendrocyte precursors with enhanced ischemic sensitivity [26–28]. This pattern of injury in the patient with CHD suggests that oxygen deprivation is the leading cause of intraoperative injury, not embolic or hemorrhagic injury as is more commonly seen in adults.

It has been assumed that improvements in hemodynamic management during cardiac surgery have the potential to mitigate neurologic injuries in children who require cardiopulmonary bypass (CPB). However, the management of CPB for infants and children has been challenging to study clinically due to wide practice variability and lack of intercenter consensus. Pump prime, flow rate, cardioplegia solutions and administration intervals, vasodilator therapy, steroid use, cooling and rewarming practices, blood gas management, hematocrit goals, electrolyte control, ultrafiltration techniques, and the use of deep hypothermic circulatory arrest (DHCA) are all integral aspects of a complex practice that forms the protocol at a given institution. Each of these can impact cerebral perfusion, but no standardization exists for any of these parameters. Therefore, understanding the consequence of altering a single aspect of bypass care is unclear, and demonstrating the optimal combination of bypass parameters is prohibitively difficult.

Due to the pressing need to improve neurocognitive outcome and poor guidance afforded by evidence-based approaches to bypass management, effort and expense have been directed toward developing perioperative neuromonitoring strategies for children who require cardiac surgery and CPB. The monitoring technologies described in this chapter have been in routine use for more than a decade, but there is no

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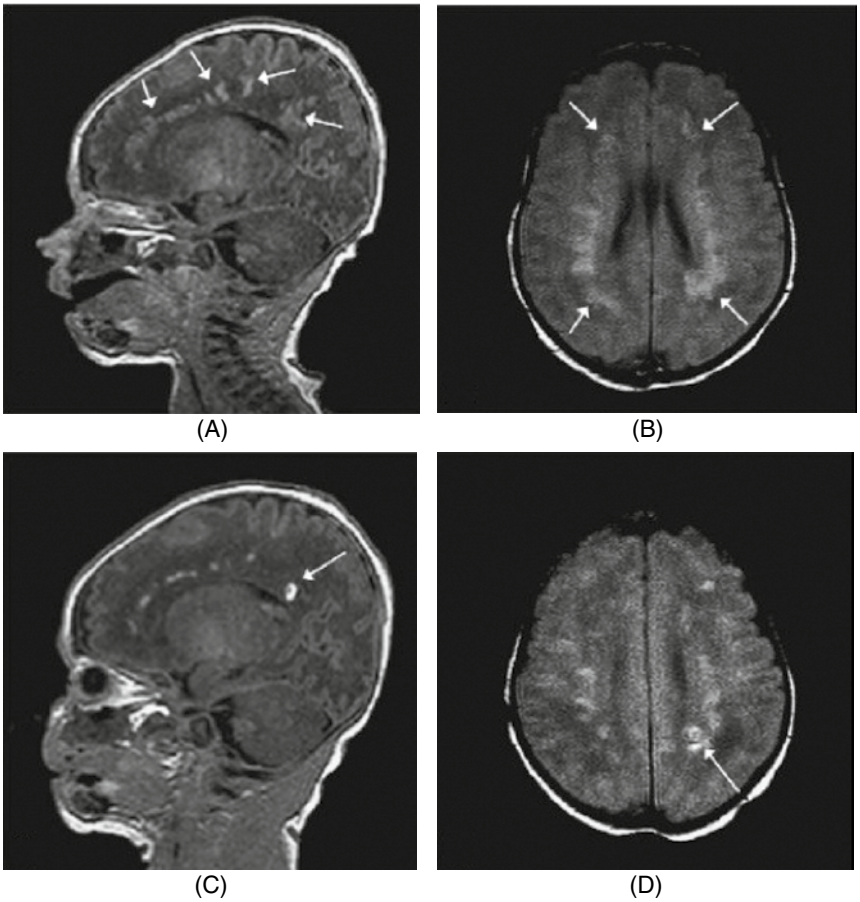


Figure 14.3 (A) Preoperative sagittal T1-weighted magnetic resonance image (MRI) of a 35-week gestational age infant with hypoplastic left heart syndrome. Significant white matter injury (WMI) is present in the periventricular areas (arrows). (B) Preoperative axial proton-density T2-weighted image. Again note the extensive WMI (arrows). (C) Seven-day postoperative T1 sagittal MRI after Norwood stage I palliation. Note the slight improvement to the WMI, but new intraparenchymal/intraventricular hemorrhage and infarction in the atrium near the body of the left lateral ventricle (arrow). (D) Proton-density T2-weighted image. Again note the WMI and new hemorrhage (arrow).

universal consensus regarding their usefulness or validity, and there is no standard of care neuromonitoring practice for the patient with CHD. This chapter reviews cerebrovascular physiology and the impact of CPB on cerebral hemodynamics, available neuromonitoring modalities, and proposed strategies for improving neurodevelopmental outcomes after congenital heart surgery.

KEY POINTS: MRI-DIAGNOSED BRAIN INJURY IN NEONATAL CARDIAC SURGERY

- Preoperative neurologic injuries occur in 20–40% of newborns with critical heart defects.
- After surgery, 35–75% of these patients will have a new brain injury.
- The most common brain lesion visible in the MRI of infants after congenital heart surgery is white matter injury (WMI), similar to periventricular leukomalacia seen in preterm infants.

Cerebrovascular physiology during cardiac surgery

Understanding cerebral perfusion and how it is affected by CPB is necessary to understand normal and abnormal neuromonitoring results during cardiac surgery. In health, cerebral perfusion regulation is known to be a finely tuned, multilayered servo control of several homeostatic mechanisms, each acting independently with regard to stimulus and frequency, but in concert at the point of action: mediating cerebral vascular resistance. These mechanisms include neurovascular coupling (also known as metabolic autoregulation), CO_2 reactivity, pressure autoregulation, hypoxic vasodilatation, hypoglycemic vasodilatation, and the uneven action of systemic vasoconstrictors to cerebral relative to noncerebral vasculature. Physiologic changes of the cerebral vasculature during bypass were largely defined by a series of studies performed in the 1980s and 1990s. Cerebral blood flow (CBF) was measured using the Kety–Schmidt technique, and CBF velocity was measured with transcranial Doppler (TCD) in both human infant and animal model studies. These efforts have highlighted the effects of extreme

hypothermia and circulatory arrest on vascular tone, CBF, and oxygen delivery and utilization within the brain.

Cooling and rewarming

During the cooling phase of CPB, CBF is reduced, and cerebral metabolism is reduced, presumably due to neurovascular coupling, which matches CBF to metabolism. However, during deep hypothermia, cerebral metabolism is exponentially reduced, while CBF is reduced linearly with reduction in temperature [29] (see Figure 14.4). This results in a state of "luxury perfusion" during hypothermia [30–33]. As shown another way, at normothermic bypass between 35.5°C and 37°C, the ratio of CBF (in mL/100g/min) to cerebral metabolic rate for oxygen consumption ($CMRO_2$, in mL/100g/min) is normal (20 : 1). At 30°C, the ratio increases to 30 : 1, and at 18°C, it increases to 75 : 1, indicating uncoupling of brain metabolism and vascular tone (see Figure 14.5) [29]. Based on the measured decrease in $CMRO_2$ in children during deep hypothermic bypass, Greeley et al. famously estimated a duration of ischemia that could be safely tolerated between 39 and 65 minutes [31]. When rewarmed after hypothermia in the absence of circulatory arrest, there is a return to normal CBF and metabolism with normal flow/metabolism coupling.

It is generally stated that cooling ablates pressure autoregulation as well as metabolic autoregulation. The two mechanisms are distinct processes that occur at distinct frequencies. Neurovascular coupling (metabolic autoregulation) is mediated by a neurovascular unit comprising an astrocyte bridge between neuronal synapses and penetrating arterioles.

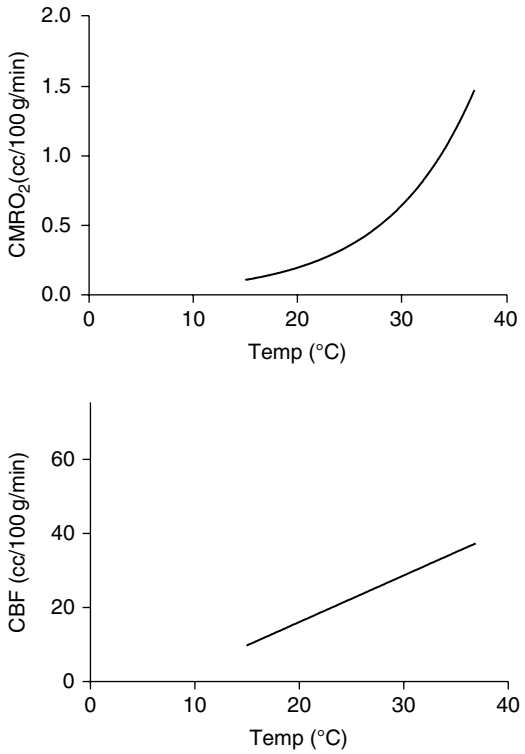


Figure 14.4 Cooling results in a linear decrease in cerebral blood flow and an exponential decrease in cerebral metabolic rate for oxygen consumption ($CMRO_2$). (Source: Adapted from Kern et al. [29].)

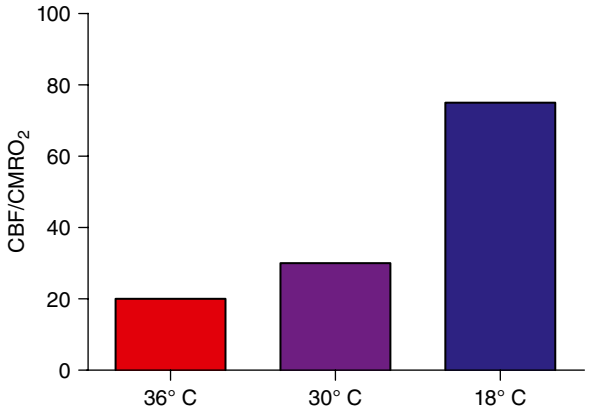


Figure 14.5 Metabolic autoregulation is attenuated with progressive hypothermia during cardiopulmonary bypass in infants. With decreasing temperature, the ratio of cerebral blood flow (CBF) to cerebral metabolic rate for oxygen consumption ($CMRO_2$) increases, yielding a luxury perfusion during hypothermia. (Source: Adapted from Kern et al. [29].)

Neurovascular coupling is spatially specific and rapidly active, effecting vascular changes within 1 second of local neuronal activation [34]. By contrast, pressure autoregulation responds to sustained changes in cerebral perfusion pressure lasting 30 seconds or longer and causes more global changes in CBF [35]. The conclusion that hypothermia also ablates pressure autoregulation comes from two independent investigations, one using TCD and the other using the Kety–Schmidt technique with xenon washout during infant bypass [31, 33, 36]. However, in both data sets, the measurements of flow or flow velocity are taken at lower cerebral perfusion pressures than those taken at normothermia, and most of the hypothermic measurements are taken below the apparent limit of autoregulation evident in the normothermic plots [37].

More recent preclinical and clinical data challenges the assumption that cooling ablates pressure autoregulation. A piglet model was used to more directly assess the relationship between deep hypothermia and pressure autoregulation. Piglets with normal arterial blood pressure demonstrated intact autoregulation, even during deep hypothermia. [38] When neonates were studied using dynamic autoregulation measurements during hypothermic bypass, the state of impaired autoregulation was accompanied, in all cases, by arterial blood pressure below the limit of autoregulation [39]. It is reasonable to conclude from this combined data that pressure autoregulation is not ablated by deep hypothermia, but rather it is impaired by the hypotensive state that frequently accompanies deep hypothermic bypass.

pH-stat vs. alpha-stat blood gas management

pH-stat management corrects blood gas values for temperature during CPB, which results in a higher arterial CO_2 tension during hypothermia than is achieved with alpha-stat blood gas management. Obviously, regardless of the measurement technique used for determining the amount of CO_2 in the blood, removing less CO_2 or adding CO_2 to the sweep gas with

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the oxygenator during bypass results in a higher arterial CO_2 tension. CO_2 diffuses freely across the blood–brain barrier, acidifying cerebrospinal fluid, which exerts a potent cerebral vasodilatory effect. The cerebrospinal fluid slowly returns to normal pH after exposure to high CO_2 levels by increased activity of carbonic anhydrase in the choroid plexus, replacing reabsorbed acidic spinal fluid with spinal fluid having a higher concentration of bicarbonate buffer. Driving CBF changes by manipulation of arterial CO_2 tension is, therefore, time limited by the rate of spinal fluid absorption and production. Spinal fluid production is slower in infants than in adults, but in adults, the entire spinal fluid volume is produced three to four times per day. Not surprisingly, then, animal models have shown that sustained changes in arterial CO_2 tension cause CBF changes that last approximately 1 day [40, 41]. In addition to increasing CBF, arterial hypercapnia shifts the oxyhemoglobin dissociation curve to the right, facilitating oxygen unloading [42]. Thus, in most pediatric centers, pH-stat (hypercapnia) strategy is favored for perceived neuroprotection.

In animal models of DHCA, neurologic outcome is improved when pH-stat is used. This has been more difficult to demonstrate in human infants, although a trend toward a lower death rate, fewer seizures, and greater hemodynamic stability has been observed [43]. Long-term neurologic follow-up at 4 years of age has not shown a difference between pH-stat or alpha-stat blood gas management, and this has only been studied retrospectively in a pediatric setting [42, 44].

Hemodilution and transfusion practices during CPB

Traditionally, profound anemia was used during deep hypothermic CPB to offset the effect of cooling on blood viscosity. This practice, rooted in theory, was challenged by demonstration of increased neurologic injury in a piglet model of hypothermic circulatory arrest using a target hematocrit of 30% when compared with a target of 20% [45]. More convincing was a randomized study of hematocrit goals at Boston Children's Hospital. The combined data from two trials at Boston included the neurodevelopmental outcomes of 271 infants at 1 year of age. The Psychomotor Development Index (PDI) increased linearly with hematocrit up to 23.5%. The Mental Development Index (MDI) did not exhibit an association with hematocrit. The overall conclusion of this analysis was that although a hematocrit higher than 24% improved outcome, the effects of hemodilution vary according to age and other parameters of perfusion, especially pH management, precluding delineation of a universally optimal hematocrit [46].

KEY POINT: HEMODILUTION DURING BYPASS

- The optimal hematocrit target for hemodilution during CPB is unknown, but hematocrit less than 24% during hypothermic bypass is associated with developmental abnormalities in the motor domain and should be avoided.

Temperature management

Hypothermia remains the cornerstone of brain protection for ischemic injury. Cerebral hyperthermia frequently develops after congenital heart surgery with CPB. The metabolic rate and oxygen consumption of the brain are raised during a period when oxygen delivery may be compromised due to hypotension. This places vulnerable watershed areas and partially injured brain tissue at risk for injury extension [47]. Bissonnette and colleagues measured temperatures in the jugular bulb, tympanic membrane, lower esophagus, and rectum during and after surgery in 15 infants and showed that the jugular bulb temperature continued to rise for at least 6 hours postoperatively [48]. The authors found that rectal temperature does not reflect cerebral temperature in the perioperative period. Other investigators further showed that nasopharyngeal and not tympanic temperature best reflects brain temperature [47]. However, Cottrell and colleagues were unable to show any association between neurocognitive performance and postoperative temperature in a cohort of 329 infants who underwent cardiac surgery [49].

In some patients, brain metabolism is not adequately suppressed during rapid cooling to deep hypothermic levels. In a study of infants undergoing cooling to 15 °C, 6 of 17 had low jugular venous bulb saturation when this temperature was achieved (87 ± 6% vs. 98 ± 1% in subjects with apparently normal cooling), suggesting ongoing oxygen consumption that outstripped delivery of oxygen to the brain [50]. There is general concern that uneven or inefficient cooling of the brain may lead to neurologic deficits. Rapid cooling times have been associated in pilot studies with developmental delay and the rare complication of choreoathetosis [51, 52]. There is little debate about the benefits of cooling during CPB, yet there is also insufficient data to suggest that any cooling strategy leads to better patient outcome [44].

Normothermic or mildly hypothermic CPB has gained popularity in recent years. Hannon and colleagues retrospectively studied 78 patients undergoing normothermic (35 °C or greater) vs. hypothermic bypass (28–34 °C) [53]. Patients were less than 2 years of age (median 7 months), and operations requiring deep hypothermia for DHCA or aortic arch reconstruction were excluded, and follow-up was 2–3 years after surgery. For both groups, the odds ratios for neurodevelopmental delay in one or more areas ranged from 2–8 times that of a normal population. After multivariable adjustment, including for genetic conditions (Trisomy 21, DiGeorge syndrome, 22q11.2 deletion syndromes), there was no difference in the incidence of neurodevelopmental delay between the groups.

Glucose management

In the Boston Circulatory Arrest Study (BCAS), hyperglycemia was not associated with worse neurologic outcome and does not appear to be a risk factor for infants and children [54]. Intraoperative glucose concentrations were not related to developmental scores up to 8 years of age, but low glucose concentrations were associated with subclinical seizure activity [55]. In a study of 188 neonates and infants younger than 6 months undergoing surgery with CPB, mean intensive care unit (ICU) admission glucose was 328 mg/dL, maximum was 340 mg/dL, and 89% of patients had at least one

value greater than 200 mg/dL. In that cohort, hyperglycemia was not associated with lower neurodevelopment scores at 1 year of age [56]. Krueger and colleagues assessed neurodevelopmental outcomes at age 4 years in 167 infants undergoing cardiac surgery with bypass as infants [57]. Fourteen percent had hyperglycemia (>145 mg/dL) in the postoperative period, and insulin was administered if the glucose value was above 216 mg/dL. Higher postoperative glucose levels were not associated with lower neurodevelopmental scores across multiple domains. Tight glucose control is not indicated by evidentiary review in children who require CPB and is likely to be harmful in this population [44].

Circulatory arrest

For infants who require reconstruction of the aortic arch, a bloodless field cannot be achieved with standard cannulation techniques. When DHCA is employed for this scenario, a profound cerebrovascular derangement occurs that persists into the rewarming and postoperative recovery periods. This cerebrovascular injury has been characterized by low $CMRO_2$ that fails to return to baseline values, low CBF (with a normal CBF:$CMRO_2$ ratio), and a distinctive TCD flow velocity pattern showing absent or reversed flow during diastole (see Figure 14.6) [58–61]. These derangements have been shown to be reduced in incidence by the use of low-flow CPB instead of circulatory arrest, delayed rewarming, the use of pH-stat blood gas management during cooling, modified ultrafiltration, thromboxane A_2 antagonism, and the administration of nitric oxide donors [59, 62–66]. Although these therapies mitigate the post-circulatory arrest physiologic derangement of the cerebral vasculature, there is no evidence that they change the incidence of periventricular leukomalacia, nor is it proven that these techniques improve the neurocognitive performance of patients with CHD.

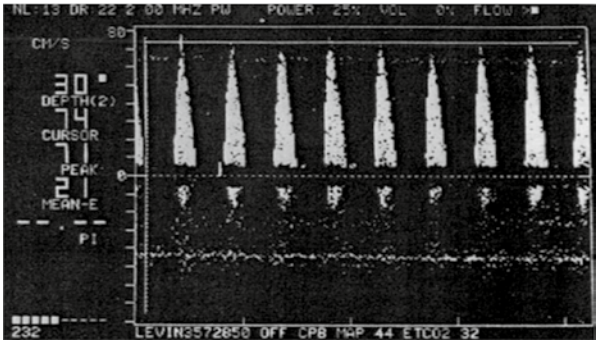


Figure 14.6 After cardiopulmonary bypass with deep hypothermia and a period of circulatory arrest, there is an absence of cerebral blood flow during diastole. This pattern of flow velocity measured with transcranial ultrasound is indicative of high cerebrovascular resistance. (Source: Jonassen et al. [58]. Reproduced with permission from Elsevier.)

KEY POINTS: DHCA

- DHCA in infants is associated with a profound cerebrovascular disturbance characterized by low $CMRO_2$ and low CBF that is absent or reversed in diastole.
- This condition persists into the postoperative period.

Selective cerebral perfusion

Selective cerebral perfusion (also termed regional low-flow cerebral perfusion, antegrade cerebral perfusion, or regional cerebral perfusion) is the surgical response to concerns that circulatory arrest causes neurologic injury. A variety of techniques achieve the same goal of delivering bypass flow to the cerebral vasculature while leaving a bloodless aortic arch for surgical repair. In one version of the technique, a polytetrafluoroethylene graft is sewn into the innominate artery and subsequently cannulated for bypass, in lieu of the traditional cannulation at the aortic root. When selective perfusion is desired, the great vessels are snared, and flow is continued at a reduced rate, now entirely directed to the circle of Willis (see Figure 14.7) [67]. It seems evident that circulatory arrest

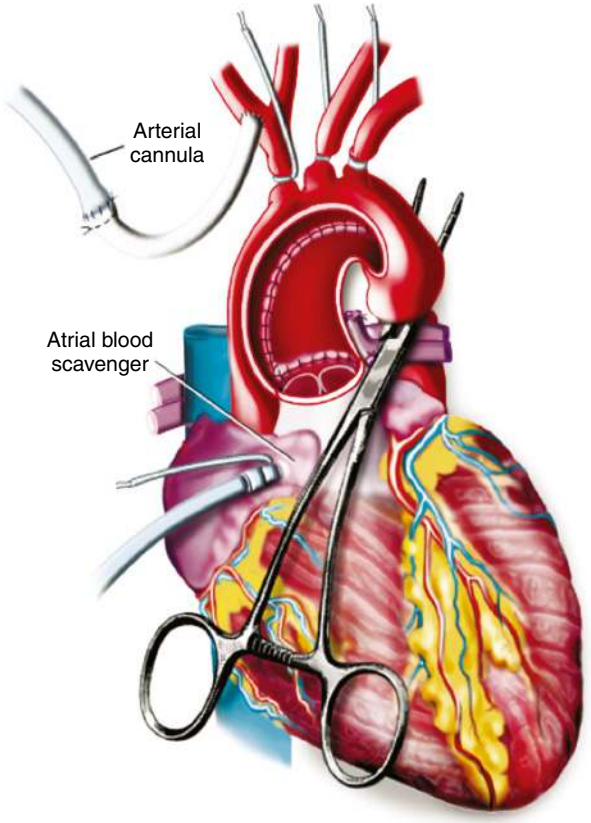


Figure 14.7 Selective cerebral perfusion performed by sewing a graft to the innominate artery and snaring the great vessels. (Source: Pigula et al. [67]. Reproduced with permission from Elsevier.)

and impaired neurovascular recovery after circulatory arrest would cause neurologic injury, but there is no agreement that circulatory arrest should be replaced with either low-flow bypass or newer techniques of selective antegrade cerebral perfusion.

For instance, neurocognitive testing of a 238-subject cohort at 4 years of age following surgery in infancy at the Children's Hospital of Philadelphia showed that the duration of hypothermic circulatory arrest was not associated with a poor

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performance in any category of the neurodevelopmental test [68]. Gaynor and colleagues argued with this result that nonmodifiable factors such as genetic anomaly, socioeconomic status, maternal education, and gestational age were overwhelmingly responsible for poor results on neurocognitive testing and that circulatory arrest is not a contributor to poor neurologic outcome. This result and interpretation contradict the most popular reading of studies related to the Boston circulatory arrest trial, which showed increased seizures and lower development scores in multiple functional domains at 1, 4, and 8 years of follow-up in subjects who underwent circulatory arrest as a randomized intervention [4, 6, 54, 69, 70]. With later testing in the teenage years of the same cohort, differences between arrest and nonarrest groups are less apparent [71]. Although the Boston circulatory arrest trial is one of the most widely studied and cited research efforts on the topic of neurologic injury and circulatory arrest, it is difficult to compare contemporary practice with the bypass strategy from 1990, which included deliberate hemodilution to a hematocrit of 20% [72].

More recently, the "Hearts and Minds" study performed in Auckland, New Zealand, and Melbourne, Australia, found that longer periods of circulatory arrest were associated with a significant increase in the severity of periventricular WMI [22] (see Figure 14.8). In the Hearts and Minds study, many nonmodifiable characteristics were more significantly associated with WMI than the use of circulatory arrest. These included the nature of the cardiac lesion and the brain maturity score. The presence of WMI was not associated with 2-year neurocognitive performance in that cohort.

Two trials comparing circulatory arrest with selective cerebral perfusion found no difference in neurocognitive outcomes at 1 year. Visconti and colleagues studied 29 subjects with HLHS who received either selective cerebral perfusion or circulatory arrest without randomization for the Norwood procedure [73]. Goldberg and colleagues studied 77 subjects with the same condition, randomized for the two bypass strategies [74]. Neither study showed significant improvements with the selective perfusion technique, but it has been argued that neurodevelopmental scores in both groups were lower than expected.

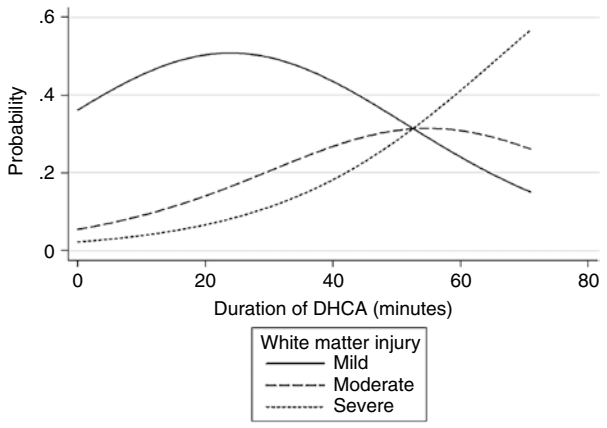


Figure 14.8 Data from the Hearts and Minds study showed that longer circulatory arrest times were associated with an increase in the severity of white matter injury. DHCA, deep hypothermic circulatory arrest. (Source: Beca et al. [22]. Reproduced with permission from Wolters Kluwer Health, Inc.)

Another randomized trial of selective cerebral perfusion vs. circulatory arrest was done with 37 neonates requiring arch reconstruction. More than 70% of subjects in both groups of that study had a new MRI injury. WMI was the most common new lesion in both groups, but 33% of the subjects in the selective perfusion group had a deep embolic stroke on the side used for selective perfusion [75]. This high rate of an unusual neurologic injury is contrasted with a cohort of 57 neonates with high-risk lesions, all undergoing selective cerebral perfusion from Texas Children's Hospital. In that observational cohort, a 40% incidence of new injury was seen, with WMI being the most common, and none had evidence of unilateral embolic load, despite a high flow rate during selective perfusion (56 ± 10 mL/kg/min). In the Texas cohort, the duration of selective perfusion was not associated with poor neurocognitive outcome, but the duration of circulatory arrest was associated with significant worsening in the cognitive domain at 1-year follow-up [8].

Selective cerebral perfusion and flow rates

Adding to the debate over whether to use hypothermic circulatory arrest or selective cerebral perfusion is the problem of choosing a flow rate when perfusing the circle of Willis directly. In the normal state of perfusion, the brain is protected from over- and under-perfusion, specifically by the mechanism of pressure autoregulation. There is evidence that pressure autoregulation is entirely pressure-driven and that cardiac output (or pump flow rates) is not relevant to cerebral perfusion as long as perfusion pressure is within the limits of autoregulation [76–78]. However, the ability of the cerebral vasculature to increase and decrease flow is at least conceptually dependent on a parallel vascular connection with the rest of the systemic circulation from which it can draw flow when vasodilating and to which it can push flow when vasoconstricting. With the great vessels snared and flow directed to the carotid artery, there is an unknown narrowing of the range of flow rates that yield pressures acceptable for cerebral perfusion. Inconceivably wide ranges of selective perfusion flow rates have been published, from 10 to 100 mL/kg/min [79, 80].

Experimental work in piglets has addressed this question. DeCampli, Myung and colleagues, and Sasaki and colleagues independently studied similarly aged infant piglets with selective perfusion techniques at different flow rates [81–83]. By recording arterial blood pressure at the limb ipsilateral to the cannulation site, it was possible to see the relationship between flow rates and resultant pressure directed to the cerebral vasculature (see Figure 14.9). Published reports of neonates studied during selective cerebral perfusion have recorded the right radial arterial blood pressure during right innominate cannulation, which allows for the same relationship to be described in humans (see Figure 14.9) [16, 80, 84–87]. Although the piglet data suggests a safe range of flow rates between 20 and 30 mL/kg/min, examination of the human data clearly shows that the piglet data cannot be translated in this manner. The human infant achieves a lower cerebral perfusion pressure for the same flow rates when compared with the piglet during selective perfusion. Further, the use of pH-stat blood gas management in the human infant increases the required flow rate, whereas pH-stat blood gas management in

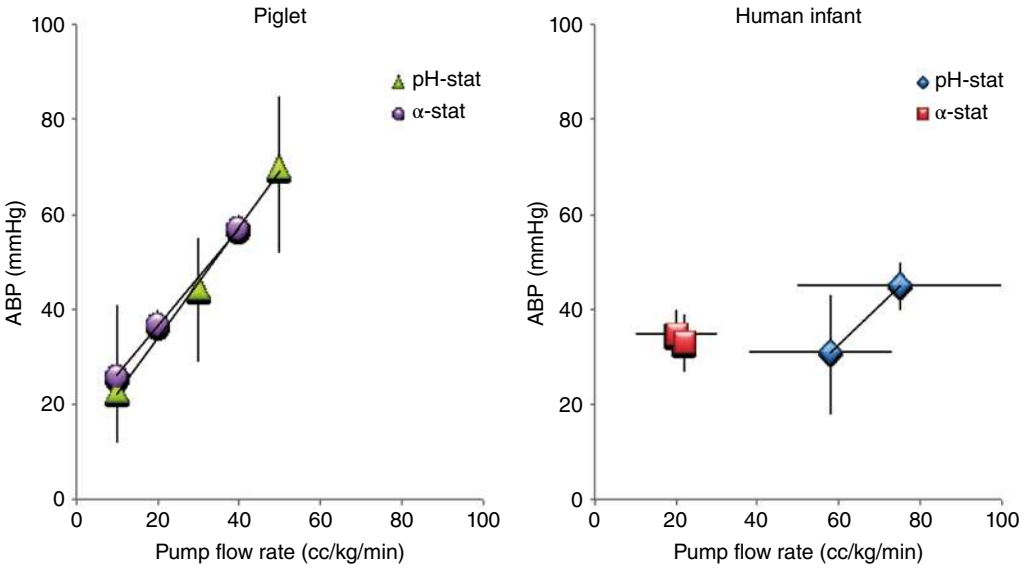


Figure 14.9 The relationships between arterial blood pressure (ABP) and pump flow rates are shown for the piglet model of selective cerebral perfusion and the human infant for two blood gas management strategies.

Table 14.1 Human vs. neonatal piglet models of selective cerebral perfusion

Study subject	Brain weight (g)	Body weight (kg)	P_aCO_2 Mgt	CBF/brain wt (mL/100 g/min)	CBF/body wt (mL/kg/min)
Piglet	60	3	α-stat	25	5
Piglet	60	3	pH-stat	60	12
Human infant	450	3	α-stat	12	18
Human infant,	450	3	pH-stat	20	30

The translation of piglet studies of cerebral perfusion is best understood after comparing the relative mass of the piglet and human brain, the relative body mass of the piglet and human infant, and cerebral blood flow expressed in standard units (mL/100 g/min), and in units relevant to perfusion (mL/kg/min). The effect of blood gas management is also shown. The human brain under pH-stat management is predicted to require six times the pump flow rate of a piglet under α-stat management. The effect of noncerebral tissue vasculature remains unknown.

the piglet does not seem to change flow rate requirements during selective perfusion.

The translation of selective perfusion data from piglet to human would require accounting for differences in brain size (60 g piglet brain, 450 g human infant brain), brain development (the piglet is born ambulating with myelinated white matter, with different metabolic requirements and CBF), as well as the ratio of cerebral to collateral systemic circulation that occurs due to anatomic differences. Given the observed response to blood gas management changes shown in Figure 14.9, one can argue that the ratio of cerebral to noncerebral perfusion in the human during selective perfusion is much higher than the piglet model of selective perfusion. The basis of this argument is that CO_2 tension changes in the blood affect cerebral vascular tone, but leave noncerebral vascular tone relatively unchanged. If the piglet had a large percentage of CBF to total blood flow during selective perfusion, the pressure would drop with pH-stat management, as it does in human infants.

CBFs during bypass have been measured in piglets and human infants under both alpha-stat and pH-stat blood gas management and are summarized in Table 14.1 to facilitate comparison of the human infant with the piglet model [33, 83, 88–92]. The piglet has a higher CBF/100 g of tissue, but pump flows are determined by body weight, not brain size. Therefore, the CBF rates/kg body weight are much smaller. These differences limit the applicability of piglet studies of selective perfusion to clinical practice.

An alternative approach has been to rely on neuromonitoring of individual patients to determine selective perfusion flow rates. The TCD is used to determine flow velocities in the middle cerebral artery after cooling, but before selective perfusion. With initiation of selective perfusion, flows are gradually increased from zero until the flow velocities are equal to the preselective perfusion values [80]. This technique results in a wide interpatient variability in flow rates, with a mean flow rate of 56 ± 10 mL/kg/min. Of 57 high-risk patients reported with this technique, 23 (40%) had a new MRI-detected brain lesion after surgery. Most lesions were WMI, and the lesions were evenly divided between ipsilateral and contralateral hemispheres with respect to the cannulation site. Nonrandomized neurodevelopmental outcomes using the Bayley Scales of Infant Development at 12 months yielded cognitive domains on a par with population norms, and language and motor domains 0.8 and 0.9 standard deviations (SDs) lower than population norms [8].

KEY POINTS: SELECTIVE CEREBRAL PERFUSION

- During selective perfusion, with the great vessels snared and flow directed to the carotid, there is an unknown narrowing of the range of flow rates that yield pressures acceptable for cerebral perfusion.
- Flow rates for selective perfusion have ranged from 10 to 100 mL/kg/min.
- A TCD and near-infrared spectroscopy (NIRS)-guided flow protocol with mean 56 mL/kg/min has been published, yielding a low rate of new MRI injury and good 12-month neurodevelopmental outcomes.

KEY POINTS: EVIDENCE-BASED MEDICINE AND PHYSIOLOGICAL MONITORING OUTCOME STUDIES

- The pulse oximeter is a mandatory intraoperative monitor despite failure of research to show any outcome benefit after randomization of nearly 23,000 subjects.
- The universal refusal of practitioners to disbelieve the apparent benefit provided by pulse oximetry casts doubt on the ability of the randomized trial to demonstrate benefit for any monitoring modality.

Neurological monitoring during congenital heart surgery

> If a man will begin with certainties, he shall end in doubts: but if he will be content to begin with doubts, he shall end in certainties.
>
> Francis Bacon, 1605 [93]

Empiricism, inductive reasoning, and the scientific method have converted medicine from mysticism to an evidence-based practice. The randomized controlled clinical trial is not new to medical science, but the modern ability to assimilate the vast catalog of medical data has been transformative [94]. The contemporary concept of evidence-based medicine by meta-analysis is a rigorous, methodical scoring of available evidence that provides a common platform for the standardization of practice [95]. Neuromonitoring has been reviewed with this matrix. In the case of all three neuromonitors presented in this chapter (electroencephalography, TCD ultrasonography, and reflectance NIRS), the final evidentiary scores were level III, i.e., no demonstrable benefit [44]. The antithesis of evidence-based practice includes two categories of offense: nonconformity to practices shown to be beneficial and adherence to practices not shown to be beneficial. While no monitoring device has been shown by this evidentiary standard to be beneficial, the American Society of Anesthesiologists continues to recommend a standard, minimum acceptable intraoperative monitoring platform to include pulse oximetry, blood pressure, and electrocardiography [96]. This breach of evidence-based practice is most pointed for the pulse oximeter, which is a mandatory intraoperative monitor despite failure of research to show any outcome benefit after randomization of nearly 23,000 subjects [97]. The universal refusal of practitioners to disbelieve the apparent benefit provided by pulse oximetry casts doubt on the ability of the randomized trial to demonstrate benefit for any monitoring modality [98]. For similar reasons, final conclusions in meta-analyses of intraoperative neuromonitoring, including those described hereafter in this chapter, are commonly upgraded in tone from "not indicated" to "may be considered," despite the inability to support this conclusion with data [44, 99].

Electroencephalographic technologies

The standard electroencephalogram (EEG) with 2–16 channels has been utilized in congenital heart surgery [100]. The EEG has a primary clinical purpose of detecting and diagnosing seizure activity. More recently, it has been used as a guide of anesthetic depth and to document electrocerebral silence before circulatory arrest [101]. EEG is affected by several factors, including anesthetic agents, temperature, and CPB. Impracticalities associated with intraoperative EEG include electrical signal interference, complexity of placement, and interpretation. Newer devices using processed EEG technology are more user-friendly and have been extensively reviewed [102, 103]. Although the value of perioperative EEG monitoring has better rationale in recent years (see below), there is conflicting outcome data. For example, neonates after stage I repair of HLHS had normal perioperative EEG findings when postoperative MRI scans showed ischemic injuries [20].

The Bispectral (BIS™) Index Monitor (Covidien, Inc., Mansfield, MA, USA) is currently promoted to guide the depth of anesthesia. BIS sensors are applied to the forehead and temple, producing a frontotemporal montage, which connects to a processing unit. The device is easy to use, and the monitor requires no calibration. The proprietary algorithm of Covidien (originally Aspect Medical Systems) renders the BIS index from one-channel processing of the EEG [104]. The BIS index ranges from 0 (isoelectric EEG) to 100 (awake), with mean awake values in the 90–100 range in adults, infants, and children [105]. While awareness is a concern with surgery requiring CPB in adults, there is a scarcity of data in the literature regarding this problem in children requiring heart surgery [106, 107]. The BIS monitor also reports a burst suppression ratio, which would, in theory, be useful to see the effect of cooling on suppression of electrical activity in the brain. However, the literature has only case reports describing this practice in pediatrics [108, 109].

In a cohort of children undergoing open heart surgery with an anesthetic tailored for "fast tracking," BIS scores increased during rewarming, a period considered at risk for awareness under anesthesia [110]. However, in that study and a similar study of infants younger than 1 year, BIS did not correlate with biochemical surrogates of light anesthesia, including stress hormones.

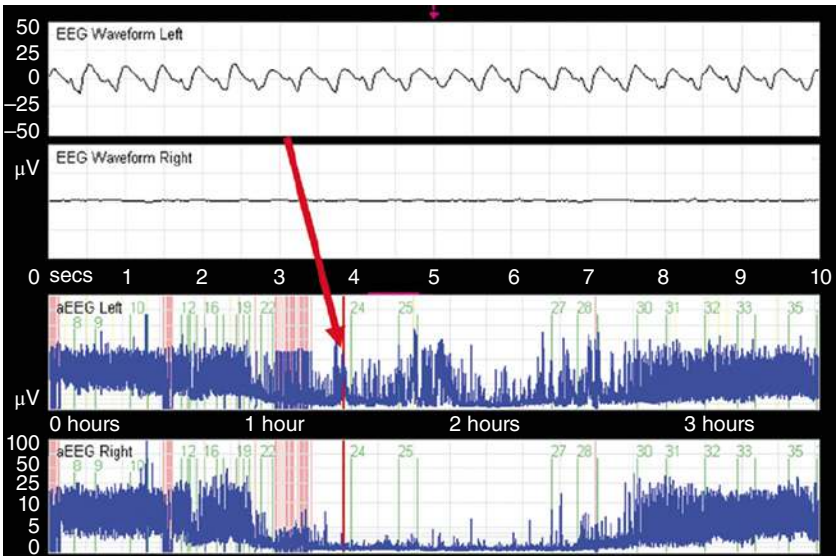


Figure 14.10 Intraoperative aEEG recording with repetitive ictal pattern indicating left-sided seizure on the raw EEG trace (top row) and corresponding to the left compressed trace (third row) highlighted by the red arrow. (Source: Gunn et al. [113]. Reproduced with permission from Elsevier.)

Andropoulos and colleagues reported a cohort of 68 neonates undergoing single ventricle (SV) and two-ventricle (2V) repairs who underwent full 11-lead neonatal EEG monitoring for 6 hours preoperatively and 72 hours postoperatively [111]. High-flow bypass with neuromonitoring including NIRS with a treatment protocol for rSO_2 <50% was utilized. Selective cerebral perfusion with transcranial Doppler-guided flow rates were also employed, and DHCA was minimized. There were no preoperative EEG seizures identified. In the 72-hour postoperative period, one patient experienced two brief EEG seizures for a total of 125 seconds; for an overall incidence of 1.5% (95% confidence interval 0.3–7.9%). This EEG seizure incidence is lower than most other cohorts (see below), and the discussion focused on targeted management of CBF and oxygenation and the fact that significant doses of benzodiazepines were administered intraoperatively and postoperatively in this population (median of about 2 mg/kg midazolam in the perioperative period), which could suppress seizures. This report emphasizes the importance of specifying anesthetic/sedative and bypass and neuromonitoring protocols when reporting EEG seizure incidence.

Amplitude-integrated EEG (aEEG) has been utilized in neonatal intensive care for two decades and has prognostic outcome value for term neonates with hypoxic–ischemic encephalopathy (HIE) and who undergo therapeutic hypothermia [112]. Four needle or adhesive electrodes plus a reference electrode are applied to yield a two-channel EEG, from two parietal and two frontal locations. The raw EEG signal is smoothed, rectified, amplitude integrated, and displayed at the bedside. The aEEG signal is evaluated for background pattern, ictal discharges, burst suppression, low voltage, or an isoelectric EEG, allowing real-time assessment and treatment. Reports of intraoperative use of aEEG for infant cardiac surgery are limited. Gunn and colleagues studied 39 neonates undergoing Norwood stage I palliation for HLHS with selective cerebral perfusion and reported intraoperative seizures in 9 (23%), predominately occurring at hypothermia of 20–24 °C [113] (Figure 14.10). Of note, NIRS was not utilized in this study nor was the CPB flow rate during selective cerebral perfusion specified (see above). Eighteen percent of this cohort experienced seizures in the early postoperative period. Seizures were not associated with later neurodevelopmental impairment at 2 years, but were associated with increased early mortality. Failure of the background aEEG pattern to return to normal by 48 hours was associated with increased early mortality and lower motor scores at 2 years. In other cohorts, postoperative abnormal aEEG patterns, consisting of seizures, abnormal background activity, and abnormal sleep–wake cycles, have been associated with new postoperative MRI brain injury after cardiac surgery in neonates and lower IQ but not motor scores at age 4 years [112, 114].

Pittet and colleagues reported 31 neonates with conventional 13- or 19-lead video EEG monitoring before cardiac surgery, and 5 (16%) experienced EEG seizures, with no clinical correlate [115]. All neonates with preoperative seizures had significant brain injury on MRI, including acute stroke, watershed injury, intracerebral hemorrhage, and WMI. Of the 157 recorded seizures, 62% were in the same area as MRI brain injury.

In a 2021 systematic review and meta-analysis of DHCA and EEG monitoring in the perioperative period for pediatric cardiac surgery, Alkhatip and colleagues reviewed 19 studies with 1,267 patients [116]. The event rate of EEG seizures was 14.9%, and seizures were associated with acute neurological findings, MRI abnormalities, and lower IQ and PDI scores on longer term follow-up. Longer DHCA times were associated with a higher incidence of EEG seizures.

While intraoperative utilization of either conventional or aEEG monitors remains limited due to complexity and space constraints, postoperative EEG monitoring for high-risk neonates and infants undergoing cardiac surgery is increasingly common, and the American Clinical Neurophysiological Society recommends continuous EEG monitoring in this patient group [117]. It seems intuitive to treat EEG seizures

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since they are clearly a manifestation of brain injury, and many centers are now doing this; whether seizure treatment and suppression will improve longer term neurodevelopmental outcomes needs to be further studied [118].

KEY POINTS: EEG TECHNOLOGIES

- EEG seizures occur in 10–25% of high-risk patients in the perioperative period in most studies.
- Most studies associate EEG seizures with adverse long-term neurodevelopmental outcomes.
- Postoperative EEG monitoring for high-risk patients is increasingly practiced.
- Outcome studies of seizure treatment are lacking.

Transcranial Doppler ultrasound

TCD ultrasonography is a sensitive, real-time monitor of CBF velocity and embolic events during congenital heart surgery. Currently available instruments utilize pulsed-wave ultrasound at 2 MHz frequency, which is range-gated, emits a power of 100 mW and has a sample volume length up to 15 mm. Typically, the middle cerebral artery is insonated during cardiac surgery, either across the fontanel or through the temporal bone window. Systolic, mean, and diastolic flow velocities are easily measured, as well as the pulsatility index, which is equal to the peak (systolic) velocity minus the end-diastolic velocity divided by the mean velocity [119].

The most challenging aspect of TCD use is setting the proper angle and depth to reliably interrogate flow velocity in the middle cerebral artery. This is facilitated by the presence of pulsatile blood flow and is therefore best done before initiation of bypass. Once located, small movements will require ongoing adjustments during the monitoring period to optimize the angle and depth of insonation. Cerebral vessels are not visualized by the ultrasound used, but are recognized by the patterns of flow velocity generated. When the temporal window is used, the bifurcation of the middle and anterior cerebral arteries is recognized in the Doppler signal by a maximal antegrade signal emanating from the middle cerebral artery and a similar magnitude retrograde signal emanating from the anterior cerebral artery. Insonation of the same vessel is necessary to effectively use the TCD during surgery, and the use of the middle and anterior cerebral arteries bifurcation allows the same region to be identified due to the simultaneous bidirectional flow signal (see Figure 14.11). The anterior fontanelle window can also be utilized in young infants, taking care to insonate the bifurcation of the anterior and middle cerebral arteries on the desired side, usually the right, and recognizing that the depth of insonation is significantly greater through this location.

TCD ultrasonography has been used extensively in pediatric cardiac surgical research to examine the cerebral physiologic responses to CPB, hypothermia, low-flow bypass, regional perfusion techniques, and circulatory arrest. These studies are discussed in the section on "cerebrovascular physiology during cardiac surgery." TCD monitoring can also be used to detect cerebral emboli, but the embolic load detected with this method has not been shown to correlate with acute postoperative neurologic deficits [120] or long-term neurodevelopmental outcomes [121]. The number of emboli detected by TCD is greatest after removal of the aortic cross-clamp, suggesting de-airing maneuvers guided by echocardiography, with Trendelenburg position; lung inflation to promote movement of air out of the pulmonary veins; and venting of the aortic root as strategies for mitigation [122]. In addition, TCD monitoring can be used to detect cannula malposition at either the superior vena cava or aortic sites, which is seen as an abrupt decrement in the middle cerebral artery flow velocity [123].

Monitors of cerebral oxygenation

Jugular venous bulb oximetry

Jugular bulb venous oximetry ($SjvO_2$) has been used in children with CHD since the late 1980s. It is considered the gold standard for the assessment of global cerebral oxygenation, against which reflectance NIRS monitors were validated. The catheter can be placed in the jugular bulb by retrograde cannulation of the right internal jugular vein, with or without fluoroscopic confirmation of catheter tip placement [91]. Alternatively, the superior vena cava can be cannulated in the surgical field after exposure [124]. $SjvO_2$ is conceptually a measure of the ratio of oxygen delivery to consumption in the brain. During bypass in adults, low $SjvO_2$ has been associated with low cerebral perfusion pressure and low $PaCO_2$, whereas high $SjvO_2$ is associated with low temperature [125]. The limited data available for $SjvO_2$ monitoring are not likely to be augmented in the future because the method is invasive and time-consuming when compared with reflectance NIRS, which renders a physiologically similar variable.

Near-infrared spectroscopy

In 1977, Frans Jobsis envisioned a neuromonitor for critically ill preterm neonates based on reflectance NIRS [126]. The "NIRO-SCOPE" he developed was first used in 1985, in the neonatal ICU at Duke University and led to the claim that [127]:

For effective measurement of cerebral oxygen sufficiency in a sick newborn, an instrument should be noninvasive, be adaptable at the bedside, not interfere with patient care, and give continuous rapid information. The signals should directly assess brain oxygen delivery and utilization and be sensitive to small changes. The NIRO-SCOPE appears to fulfill these basic requirements.

The technology developed by Jobsis and his colleagues has evolved into at least eight US Food and Drug Administration (FDA)-approved devices: INVOS™ 5100C and 7100 (Medtronic/Covidien, Mansfield, MA, USA), Fore-Sight® (CASMED®/Edwards, CAS Medical Systems, Inc., Branford, CT, USA), Equanox™ 3- and 4-wavelength versions (Nonin Medical Inc., Plymouth, MN, USA), CerOx™ (Ornim Inc., Dedham, MA, USA), NIRO®-200NX (Hamamatsu Photonics, Hamamatsu City, Japan), and O_3 Regional Oximetry (Massimo, Irvine, CA, USA), of which all except the CerOx are currently also approved for pediatric use. All devices utilize similar technology and are susceptible to similar artifacts and pitfalls [128].

Cerebral oximeters include a sensor placed on the forehead below the hairline. Near-infrared light penetrates human tissues, including bone, without ionization. Light in this spectrum is, however, absorbed by specific biologic chromophores

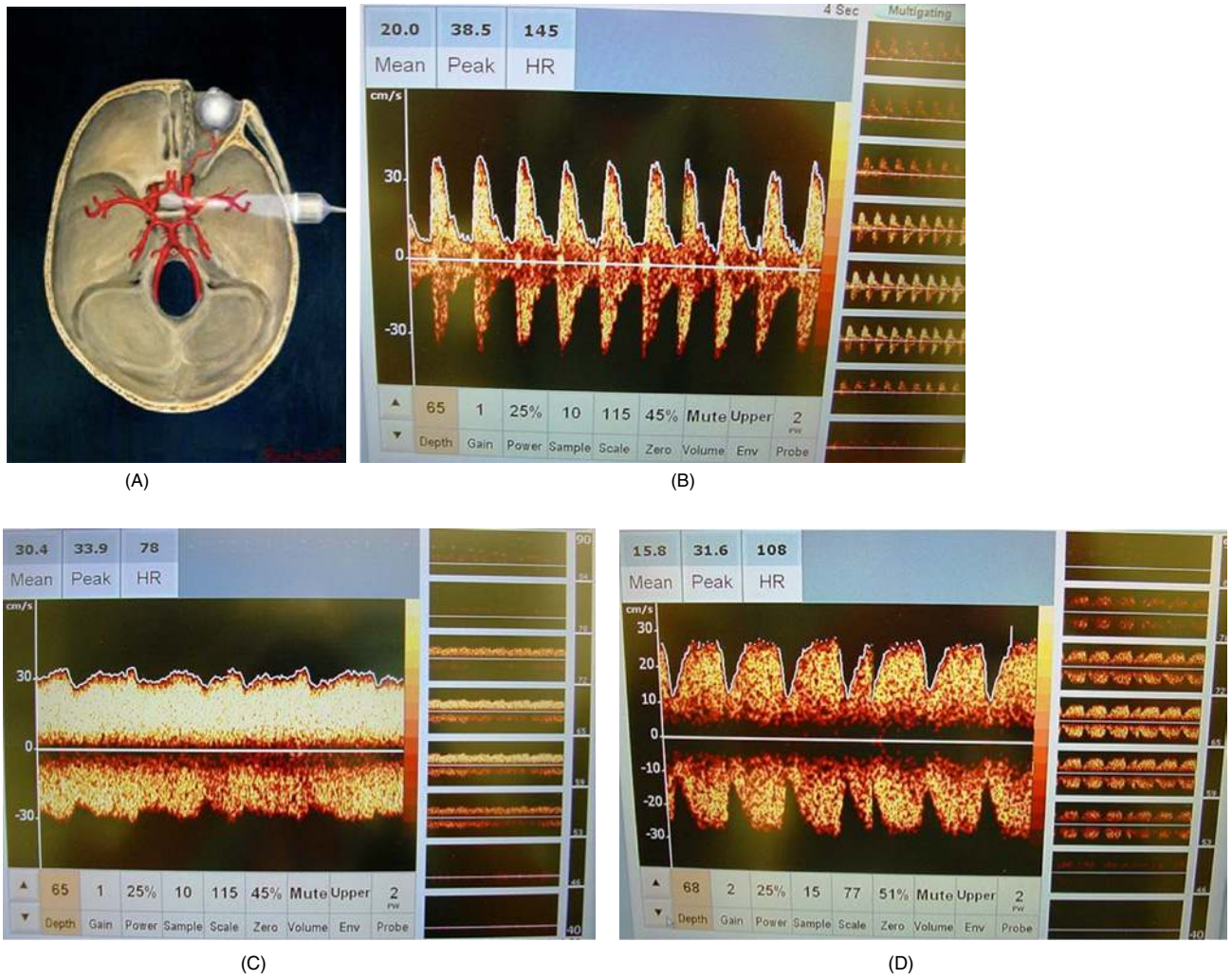


Figure 14.11 (A) The bifurcation of the middle and anterior cerebral arteries is insonated by transcranial Doppler through the temporal bone window. (Source: Runeaaslid / Wikipedia / CC BY 3.0, https://commons.wikimedia.org/wiki/File:Transcranial_doppler.jpg) (B) Transcranial Doppler waveform pre-bypass. Note in the biphasic pattern, the flow velocity above zero baseline is toward the transducer (middle cerebral artery) and the velocity below zero is away from the transducer (anterior cerebral artery). Mean and peak velocities in cm/s are displayed. The panels on the right of screen are multigating patterns at different depths of insonation. (C) Flow velocity on full flow bypass at 150 mL/kg/min. Note the nonpulsatile flow. (D) Flow velocity during selective cerebral perfusion at 60 mL/kg/min. Note the quasi-pulsatile flow pattern synchronous with revolution of the roller pump head. HR, heart rate.

(i.e., hemoglobin and cytochrome oxidase AA_3), with molar absorptivity that is dependent on the state of oxidation of the chromophore (see Figure 14.12).

When near-infrared light, whether originating from a laser or a light-emitting diode, is applied to the human forehead, it passes through tissue in all directions, refracting off various tissue interfaces such that a portion of the light returns to the surface where it can be detected. In the laboratory, using a cuvette and spectrophotometer, the Beer–Lambert equation is used to calculate the concentration of a single chromophore based on absorbance (A). Absorbance is calculated from the relative intensities of recovered (I) and incident (I_0) light passing through a cuvette in a spectrophotometer:

$$A = -\log\left(\frac{I}{I_0}\right) = \varepsilon_\lambda LC$$

where A is absorbance, ε_λ is the molar absorptivity of the chromophore at the specified wavelength of light, L is the path length of light, and C is the concentration of the chromophore in the cuvette. Naturally, hemoglobin does not occur within cuvettes in the brain, and the path length of reflected light encountering the cerebral cortex from the forehead can only be estimated. However, when multiple wavelengths of light are used, the ratio of oxygenated hemoglobin concentration to total hemoglobin concentration can be calculated, effectively cancelling unknown and estimated factors. Proprietary variations on these principles exist to account for scattering of light outside the interoptode arc, absorption by nonhemoglobin species, and extracranial (noncerebral) absorption for each of the marketed devices.

Regional cerebral oximetry is thought to describe the oxygen saturation of frontal cortical blood that is 70% venous, 5% capillary, and 25% arterial. Thus, cerebral oximetry is venous

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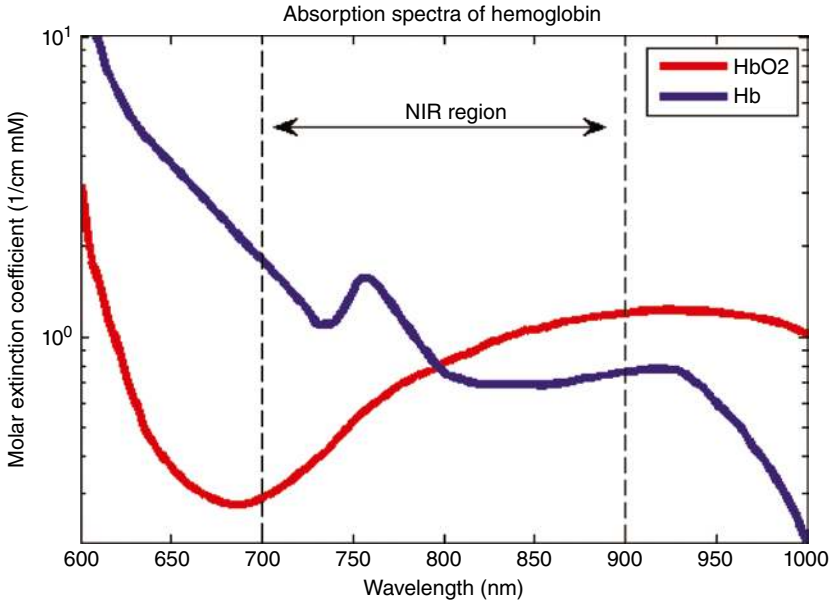


Figure 14.12 The absorption spectra of hemoglobin and oxyhemoglobin in the near-infrared (NIR) range. At the isosbestic wavelength of 805–810 nm, hemoglobin and oxyhemoglobin have similar absorption. Above this wavelength, oxygenated hemoglobin has greater absorption, and below this wavelength, hemoglobin has greater absorption. (Adrian Curtin / Wikimedia Commons / CC BY-SA 3.0, https://commons.wikimedia.org/wiki/File:Oxy_and_Deoxy_Hemoglobin_Near-Infrared_absorption_spectra.png.)

weighted, but with some arterial contribution making it consistently higher than, but trending with, jugular venous oximetry [129–131]. In piglets during CPB including hypothermic circulatory arrest, the correlation between jugular venous oximetry and cerebral oximetry was strong ($r = 0.91$) [132]. Clinical replication of this data was significant, albeit less robust [131, 133, 134]. Critics of cerebral oximetry have not challenged the evidence that cortical oxygenation can be measured with reflectance NIRS. Rather, the relevance to outcome, potential to misguide management, and justification of cost have been the questions raised by evidentiary review [44]. Some highlights of the numerous observational studies showing an association between low cerebral oximetry and neurologic injury or neurocognitive outcome are discussed below. Figure 14.13 displays bilateral regional cerebral oxygen saturation (rSO_2) intraoperatively in a neonate undergoing stage I palliation for HLHS.

A prospective study of 250 children with EEG, TCD, and cerebral oximetry monitoring during cardiac surgery showed that cortical desaturation (cerebral oximetry reductions of 20% from baseline) was the most common monitoring event. Postoperative neurologic abnormalities, including seizures, speech, movement, and visual disturbances, occurred in 26% of subjects with neuromonitoring abnormalities that were not treated. By comparison, neurologic sequelae were observed in only 6% of subjects with monitoring events that were treated and in 7% of subjects with no monitoring abnormalities [98]. Pre- and post-Norwood procedure brain MRI data from 22 subjects showed an association between new lesions and prolonged cortical desaturation [20]. Another cohort of 53 neonates with diverse congenital heart lesions showed an association between cortical desaturation and new brain lesions detected by MRI [135]. Using a mixed outcome metric combining length of ICU stay, need for extracorporeal membrane oxygenation (ECMO), and death, an association was found between 48-hour mean cerebral oximetry measurements and poor outcome in 50 neonates after Norwood for HLHS [136].

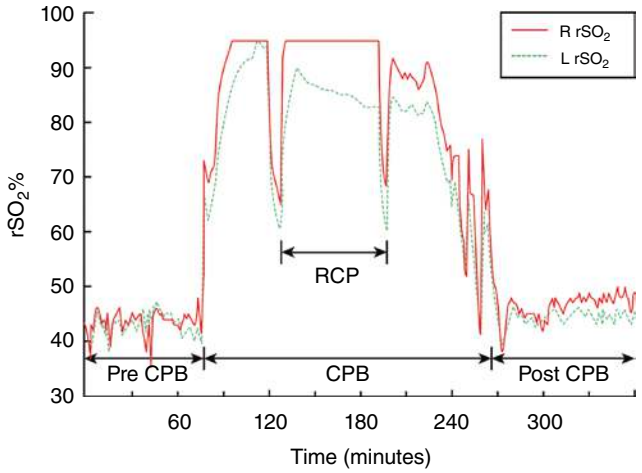


Figure 14.13 Bilateral regional cerebral oxygen saturation (rSO_2) in a neonate during stage I palliation for hypoplastic left heart syndrome. During pre-cardiopulmonary bypass (CPB) the baseline rSO_2 is low at 40–50% and similar in both frontal cerebral hemispheres. During CPB, cooling rSO_2 increases to greater than 90% bilaterally, decreasing briefly to 60–70% during deep hypothermic circulatory arrest (DHCA) for the atrial septectomy and increases again with left rSO_2 lower that right during regional cerebral perfusion (RCP). A brief period of DHCA to transfer the aortic cannula to the neoaorta is followed by increase to rSO_2 >85% and then decrease during rewarming on bypass. After bypass, rSO_2 is 45–50%.

Recent publications report additional surgical cohorts that associate low perioperative NIRS values with later decrements in neurodevelopmental outcomes. Carra and

colleagues studied 87 infants with median age of 4 months undergoing cardiac surgery with bypass and found that higher "dose" of cerebral desaturation below rSO_2 of 65% (% below 65% × minutes) in the first 24 hours after surgery was associated with lower IQ scores 2 years later [137]. In a cohort of 56 neonates with SV and 2V lesions studied by Andropoulos and colleagues, multivariable analysis of risk factors reported an association of lower preoperative rSO_2 values with lower cognitive and motor scores at 12 months [138]. Hoffman and colleagues reported that among 178 children undergoing SV or 2V cardiac surgery as neonates, lower baseline rSO_2, but not pulse oximeter-derived SpO_2, measured at the time of neurodevelopmental assessment, was a risk factor for lower motor scores from 6 to 36 months of age [139]. Aly and colleagues report 75 SV and 2V neonates who had Bayley Scales of Infant Development-II (BSID-II) testing at 6, 15, and 21 months after surgery. Patients with poor outcomes (death or a BSID-II score more than 2 SD below norms) had lower cerebral tissue oxygenation index at 60 minutes (48 vs. 58%, $p = 0.003$) and 24 hours after bypass (49 vs. 59%, $p < 0.01$) [140].

Monitoring and supporting cortical oxygenation during cardiac surgery are conceptually similar to "goal-directed therapy," used for shock management in the ICU [141, 142]. Recognition of cortical desaturation promotes interventions that increase oxygen delivery; thus, cerebral oximetry monitoring acts as a unidirectional influence on bypass practices toward higher hematocrit, higher flow rates, higher cerebral perfusion pressure, higher arterial carbon dioxide tension (pH-stat management), and the use of selective perfusion techniques [96]. Table 14.2 shows abnormalities associated with cortical desaturations and interventions performed at Texas Children's Hospital for cortical desaturation events.

Table 14.2 Causes and treatments of cortical desaturation used at Texas Children's Hospital

Abnormality	Principle	Intervention
Cerebral perfusion pressure	The brain is perfused by pressure, not cardiac output. However, our preference is to treat low pressure with cardiac output support, to avoid excessive vascular resistance and hypoperfusion of the noncerebral vascular beds.	During CPB: Increase flow rate and maintain afterload reduction. Vasopressor only if excessive vasoplegia is suspected. Check SVC and aortic cannulae. Off CPB: Administer volume judiciously with monitoring of atrial filling pressures. Inotropic support to improve stroke volume. Pacing for bradycardia. Vasopressors when excessive vasoplegia is suspected, and judiciously when volume is not tolerated and/or arrhythmia precludes beta agonist therapy.
Anemia	Low oxygen carrying capacity increases vulnerability to watershed white matter injury. The infant heart has low tolerance for the volume administration of transfusion immediately after bypass.	Avoid excessive hemodilution during hypothermia, typically 30–35%. Blood transfusion and hemofiltration during cardiopulmonary bypass to a hematocrit greater than 40% at separation. Higher hematocrit at separation allows for a volume-neutral exchange transfusion of platelets if needed.
Fever	High brain temperatures increase $CMRO_2$. High global extractions yield low mixed venous oxygen saturations, affecting arterial saturation in infants with mixing lesions.	Fevers are treated with antipyretics. Cooling is easily controlled on CPB. After separation and in the ICU, cooling can be accomplished to normothermia when needed with adequate sedation.
Hypoxia	Arterial hypoxia in the infant with a mixing lesion must be addressed systematically. Reflex administration of oxygen in this setting can result in systemic hypoperfusion.	Lung ventilation and perfusion: tracheal suction, recruitment maneuvers. Pulmonary to systemic flow ratio: evaluate for shunt occlusion, pulmonary vascular tone elevation. Mixed venous desaturation: see below
Mixed venous desaturation	Infants with mixing lesions are especially vulnerable to decrements of mixed venous oxygen content. Systemic vascular tone is the most common cause. Excessive work of breathing, agitation, shivering, and fever can contribute to low mixed venous saturation.	Alpha blockade is used for infants during cardiopulmonary bypass. Afterload reduction with milrinone, nipride, or ACE-inhibitors is a preferred first-line therapy after separation from CPB. Intubation, sedation, or paralysis may be necessary in the ICU depending on the acuity. Pressure support trials causing low mixed venous oxygen saturation and cortical desaturation should be terminated.
Hypocarbia	Arterial CO_2 diffuses freely into the CSF while soluble buffers do not. Cerebral blood flow is increased by acidic CSF (increased CO_2) and decreased by basic CSF (decreased CO_2). CSF buffering over several hours compensates acute changes cerebral blood flow caused by arterial CO_2 tension.	Whether pH-stat or α-stat methods of measuring arterial CO_2 tension are used, low cerebral blood flow can be mitigated during cardiopulmonary bypass by permissive hypercapnia.

AL Grawany

Frequency-domain NIRS and diffuse correlation spectroscopy

Frequency-domain NIRS combined with diffuse correlation spectroscopy (DCS) extends the capabilities of standard NIRS monitoring and can be utilized to measure cerebral oxygenation and hemodynamics noninvasively. CBF, cerebral blood volume (CBV), cerebral oxygen saturation (rSO_2), cerebral oxygen extraction fraction (OEF), and an estimation of cerebral metabolic rate for oxygen ($CMRO_2$) can be derived. Although primarily a research tool, its portable nature could potentially make it a clinical bedside/operating room modality, augmenting or replacing the NIRS monitors currently in use. Technical explanations of the FD-NIRS/DCS approaches are contained in recent reviews [143]. CBF measured by DCS also correlates with bypass pump flow, and TCD measured CBF velocity during full-flow bypass, low-flow bypass, selective cerebral perfusion, and DHCA [144].

Cheng and colleagues studied 31 CHD neonates (7 two-ventricle, 11 transposition of the great arteries (TGA), 13 SV) preoperatively and postoperatively and compared cerebral oxygenation and hemodynamics to 13 control neonates [145]. Preoperatively, all three CHD groups exhibited lower rSO_2 than normal controls, and the TGA and SV groups had increased OEF. The SV group had lower CBF than normal controls. Postoperatively, TGA patients had higher rSO_2 and lower CBF, OEF, and $CMRO_2$. The 2V patients had lower CBF, and the SV patients had lower rSO_2 (Figure 14.14). The same group utilized FD-NIRS/DCS to assess CBF and $CMRO_2$ during bypass in neonates and demonstrated that this noninvasive method documented the same uncoupling of CBF and $CMRO_2$ during deep hypothermia, as Greeley and colleagues measured over 30 years previously using invasive techniques (see above) [146] (Figure 14.15).

KEY POINTS: MONITORS OF CEREBRAL OXYGENATION

- NIRS technology is a well-established accurate monitor of cortical oxygen saturation.
- Accumulating data associates low rSO_2 in the perioperative period with worse neurodevelopmental outcomes.
- FD-NIRS/DCS is a noninvasive method used to assess cerebrovascular hemodynamics and $CMRO_2$.

Monitors of cerebral autoregulation

As described above, cerebral pressure and flow autoregulation is abnormal both during and after CPB in neonates and infants. Abnormal cerebrovascular pressure autoregulation in premature neonates and pediatric brain trauma patients is associated with further cerebral injury and poor outcomes [147, 148]. Outcome studies of cerebral pressure autoregulation in neonates and infants undergoing cardiac surgery with bypass are lacking, but recent developments may allow real-time bedside autoregulation monitoring and thus allow treatment strategies and facilitate outcome studies. NIRS can measure a blood volume index, which is the mathematical inversion of the optical density of light at 805 nm wavelength measure from the NIRS monitor (1-OD 805 nm). This parameter correlates with the total hemoglobin, i.e., blood volume, in the light path [149]. When correlated with mean arterial pressure derived from an arterial catheter, the hemoglobin volume index, HVx, can be derived to measure cerebral pressure autoregulation in real time, and this parameter demonstrates strong correlation with other measures of cerebral autoregulation, including laser Doppler and transcranial

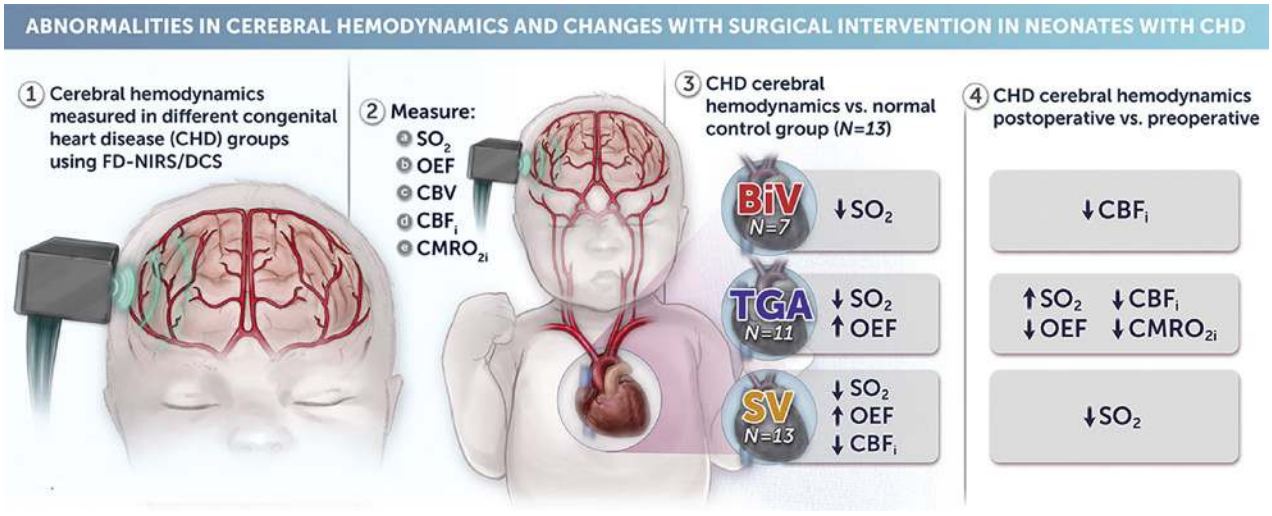


Figure 14.14 Noninvasive measures of cerebral hemodynamics and oxygenation FD-NIRS/DCS technology show significant differences between controls and CHD groups. Significant diagnosis-specific changes existed between preoperative and postoperative states. CHD, congenital heart disease; FD-NIRS, frequency-domain near-infrared spectroscopy; DCS, diffuse correlation spectroscopy; SO_2, cerebral oxygen saturation; OEF, cerebral oxygen extraction fraction; CBV, cerebral blood volume; CBFi, cerebral blood flow index; CMRO2i, ceragram metabolic rate for oxygen index; Bi-V, two-ventricle heart disease without transposition; TGA, D-transposition of the great arteries; SV, single ventricle. (Source: Cheng et al. [145]. Reproduced with permission from Elsevier.)

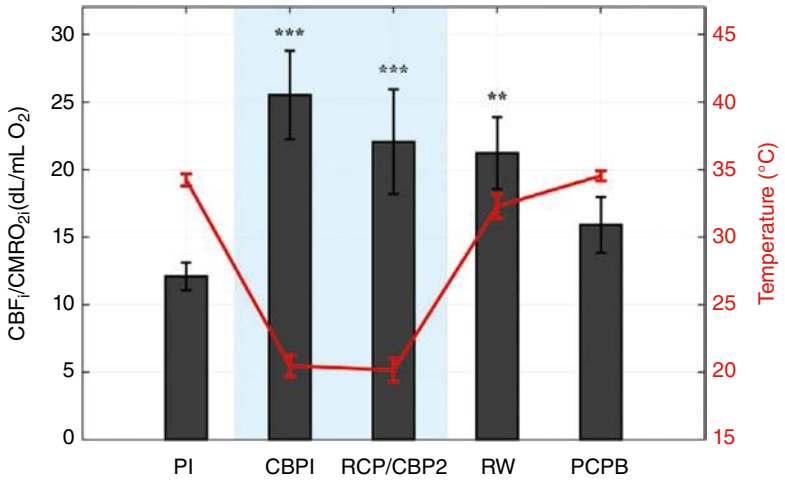


Figure 14.15 Coupling between cerebral blood flow and oxygen consumption during cardiac surgery. Mean nasopharyngeal temperature is overlaid at each stage. Note considerable increase in the CBFi/CMRO$_2$i ratio, or decrease in oxygen extraction, during deep hypothermia relative to the PI period. Error bars represent standard error of the mean values, blue shaded region are measurements during deep hypothermia, and red line is temperature. Asterisks denote significant differences from baseline. PI, postinduction; CBP1, first bypass period; RCP/CPB2, regional cerebral perfusion/second bypass period; RW, rewarming; PCPB, post bypass period. (Source: Ferradal et al. [146] / Springer Nature / CC BY 4.0.)

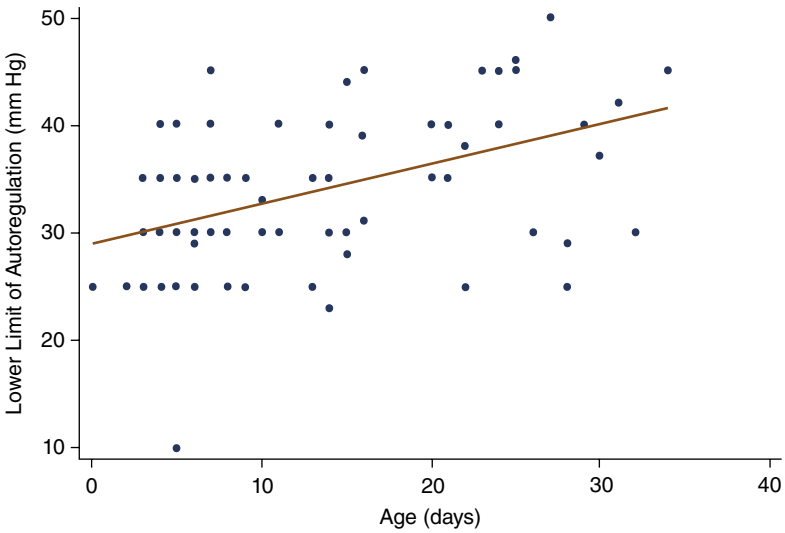


Figure 14.16 The upward trend in the first month of life for the average lower limit of autoregulation during cardiopulmonary bypass. (Source: Andropoulos et al. [151]. Reproduced with permission from Elsevier.)

ultrasound Doppler blood flow, in experimental animals [150]. HVx has a value of −1 to +1, and when autoregulation is functional, HVx has a value near zero or negative, because blood pressure and CBV are either poorly or negatively correlated. When blood pressure is outside the limits of autoregulation (either too high or too low), HVx is increasingly positive and approaches +1 because blood volume is pressure-passive, i.e., increases with increasing blood pressure and decreases with decreasing blood pressure. Because the blood volume index is already measured by NIRS monitors, efforts are under way for the FDA and other regulatory agencies to approve this monitoring modality; the advantage of this method is that no new monitoring equipment is needed, only the computer software to integrate the signals and display the HVx.

Smith and colleagues evaluated cerebral pressure autoregulation utilizing the HVx in 72 neonates undergoing surgery with bypass and assessed this parameter at different levels of hypothermia down to 18 °C [39]. Although HVx could be derived in all patients and dysautoregulation was demonstrated in all patients at hypothermia, this was confounded by the fact that mean arterial pressure decreased and exhibited collinearity with low temperature; thus, the effect of hypothermia on autoregulation could not be definitively established. In these patients, the lower mean arterial pressure limit of autoregulation ranged from 25 to 45 mmHg, with a trend upward in the first month of life [151] (Figure 14.16). Easley and colleagues measured HVx in 57 patients undergoing surgery with bypass aged from neonate to 17 years and demonstrated cerebral

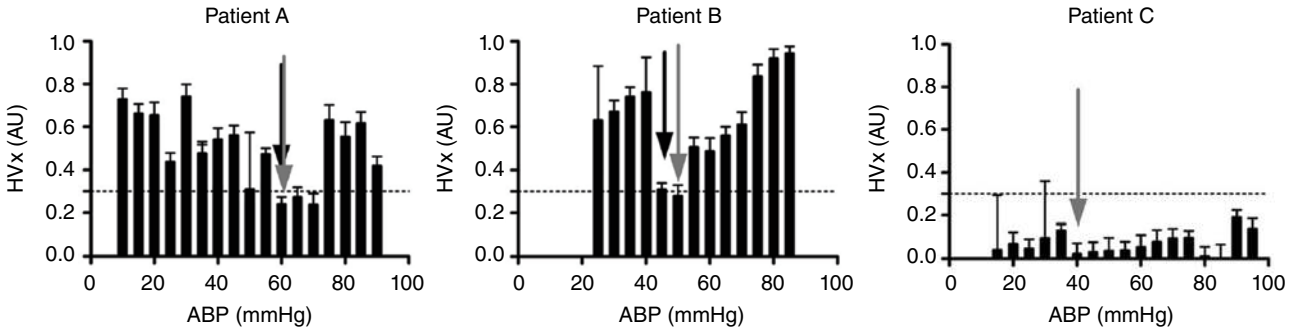


Figure 14.17 Examples of individual autoregulation curves for three different patients, one in each panel. In each graph, binned averages of the hemoglobin volume index (HVx) are plotted against arterial blood pressure (ABP) with their standard errors. The horizontal line at 0.3 for the HVx indicates the suspected threshold for loss of autoregulation. Patients were randomly selected to illustrate the identification of the lower limit of autoregulation (LLA) and the optimal arterial blood pressure (ABP opt) from the autoregulation curve. LLA is indicated with a black arrow and ABP opt with a gray arrow on each curve, as applicable. Patient A: A 7-month-old infant with Tetralogy of Fallot (TOF) undergoing complete repair. The figure demonstrates an individual's HVx curves that meet criteria for determining both an LLA and ABP opt. On the basis of the curve, the patient maintained autoregulation to an ABP of 60 mmHg, but then lost autoregulatory function with a further drop in ABP to 55 mmHg. The lowest HVx value (ABP opt) was also at 60 mmHg. Patient B: A 2-year-old child with heterotaxy undergoing bidirectional cavopulmonary shunt. The HVx curve demonstrates both LLA at 45 mmHg and ABP opt at 50 mmHg. Patient C: 3-month-old infant with TOF undergoing complete repair. This patient's HVx curve fails to meet criteria for demonstrating an LLA as all measurements demonstrate intact autoregulation. ABP opt was 40 mmHg. (Source: Easley et al. [149]. Reproduced with permission from Cambridge University Press.)

pressure dysautoregulation in many patients during CPB with an average lower limit of autoregulation of about 40 mmHg [149] (Figure 14.17). Patients with the highest peak glial fibrillary acidic protein (GFAP) (a marker of cerebral injury) values had higher peak values of the HVx, demonstrating a correlation between dysautoregulation and this marker of brain injury. Cabrera and colleagues studied 16 infants undergoing bidirectional cavopulmonary connection and reported that hypertension and elevated pulmonary artery pressure were associated with elevated HVx (cerebral pressure dysautoregulation) [152].

These studies demonstrate the potential to monitor real-time cerebral pressure autoregulation during pediatric cardiac surgery and make possible interventional outcome studies. A maneuver as simple as increasing or decreasing mean arterial pressure until intact autoregulation occurs can be compared in a randomized prospective trial to usual clinical management without autoregulation monitoring. Short-term outcomes such as neurological morbidity, MRI findings, and biomarkers of brain injury and long-term outcomes such as neurodevelopmental outcomes, can be studied. In the adult cardiac surgery population, a retrospective study demonstrated that increasing time with blood pressure below the lower limit of autoregulation was associated with major postoperative morbidity, including stroke and mortality [153]. Such a controlled trial has been performed in adults and demonstrates that when blood pressure is personalized to achieve cerebral pressure autoregulation, that postoperative delirium and memory dysfunction is reduced, although acute neurologic injury such as stroke, MRI change, and coma were not different [154]. The appeal of personalizing blood pressure to achieve autoregulation and improve outcomes is intuitive, but significant research must be done to determine whether this approach will improve neurological outcomes in infants and children [155].

KEY POINTS: MONITORS OF CEREBRAL AUTOREGULATION

- The HVx derived from NIRS can monitor pressure autoregulation in real time.
- The lower limit of autoregulation can be determined from HVx.
- Personalized blood pressure management can improve autoregulation.
- Outcome studies of autoregulation management are lacking.

Anesthetic and sedative neurotoxicity

More than 20 years ago, preclinical animal model data about neurotoxic effects of anesthetic and sedative agents that bind *N*-methyl-D-aspartate (NMDA) receptors as antagonists, and gamma-aminobutyric acid (GABA) receptors as agonists, was published [156, 157]. Increased neuroapoptosis in the developing nervous system is the predominant mechanism of injury, and this effect has been demonstrated in hundreds of preclinical publications in animal species ranging from nematodes, to rodents, to non-human primates [158]. Functional deficits in behavior, memory, and cognition have also been demonstrated. While the animal data is convincing, human data is mixed, with some observational and retrospective studies demonstrating neurodevelopmental deficits, while others do not. The recent GAS, PANDA, and MASK studies did not demonstrate a cognitive deficit (e.g., IQ) with volatile general anesthesia vs. controls for noncardiac surgery, but there were subtle decrements in behavior and executive function with a single brief exposure, and

differences in processing speed and executive function with multiple anesthetic exposure [159–162].

Primarily based on the preclinical animal data, the FDA issued a Drug Safety Communication (DSC) in 2016 warning that "repeated or lengthy (>3 hours) use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years . . . . may affect the development of children's brains" [162]. The labeling of all common anesthetic and sedative drugs, including volatile anesthetics, benzodiazepines, propofol, barbiturates, and ketamine, was updated to reflect this warning. Although this DSC has been controversial for many researchers and clinicians because of perceived paucity of human data, many congenital heart surgery patients are included this patient category of prolonged anesthesia at a young age. In addition, many patients receive prolonged sedation with GABA- and/or NMDA-binding agents postoperatively in the ICU. Dexmedetomidine has a different mechanism of binding as a presynaptic alpha-2 agonist and does not cause the same degree of neuroapoptosis at clinically relevant dose levels in the majority of animal studies, including non-human primates [163]. However currently, there are no published studies in infants and children to validate this experimental observation.

Data from three congenital heart surgery cohorts has been published to address the issue of anesthetic and sedative exposure and neurodevelopmental outcomes. The Texas Children's cohort of 59 neonates undergoing both SV and 2V repairs reported an association of larger total volatile anesthetic dose (MAC-hours) with lower neurodevelopmental scores at age 1 and 3 years [138]. The Children's Hospital Philadelphia cohort of 96 HLHS patients demonstrated an association with larger volatile anesthetic dose and lower full-scale IQ (FSIQ) and verbal IQ at 4 years [164]. Finally, the Western Canadian cohort of 95 neonatal cardiac surgery patients who underwent a comprehensive battery of neuropsychological tests at 4 years in multiple domains reported the number of days on chloral hydrate was associated with lower performance IQ and cumulative dose of benzodiazepines with lower visual motor integration scores [165, 166]. This study is limited primarily by the fact that drug exposure was calculated only for the first 6 weeks of life.

The large number of risk factors and the high incidence of neurodevelopmental deficits in the congenital heart surgery population make it difficult to design trials or studies of anesthetic and sedative neurotoxicity in this group because of the many confounders present in each of these patients. Whether alternative drug strategies, i.e., dexmedetomidine, would be associated with improved neurodevelopmental outcome, has yet to be studied. Despite its complexities, this area of research needs additional studies as potentially modifiable factors to improve neurodevelopmental outcome.

KEY POINTS: ANESTHETIC AND SEDATIVE NEUROTOXICITY

- GABA- and NMDA-binding sedatives and anesthetics cause neurodegeneration in animal models.
- Brief human noncardiac anesthetic exposures do not cause cognitive deficits, but have some associations with behavioral changes in some studies.
- There are two studies associating higher volatile anesthetic exposure in infancy with adverse neurodevelopmental outcomes in CHD.
- More data is needed, and the CHD population is difficult to study because of the multiple confounding factors.

Longer term neurodevelopmental testing outcomes after congenital heart surgery

The preceding discussion has focused on cerebrovascular physiology and neuromonitoring methods and acute or short-term neurological injury and outcomes. A number of longer term studies, e.g., 12 months to 16 years, have been published in the CHD population. These data are mostly generated from single-center cohorts of neonates and young infants studied prospectively after complex congenital heart surgery. There are several recent multicenter or combined studies that provide new data. These cohorts provide important insights into risk factors for the lower neurodevelopmental scores observed in 30–50% of neonates undergoing cardiac surgery, as they reach school age and beyond. The neurodevelopmental characteristics of this population often include deficits in cognitive, memory, language, fine motor, behavior, attention, and executive functioning domains, with a neurodevelopmental signature similar to that observed in former preterm infants [167]. Gross neurological deficits such as hemiparesis, choreoathetosis, and profound developmental delay are observed infrequently in the modern era [168, 169].

Boston circulatory arrest study

The BCAS is a landmark study initiated in the late 1980s that has set the standard for study of long-term neurodevelopment in a substantial cohort from a single center, with detailed neuropsychiatric testing and MRI brain imaging now reported in 16-year-old in the study. A total of 170 neonatal dextro-transposition of the great arteries (D-TGA) patients undergoing the arterial switch operation from 1988 to 1992 were enrolled and randomized to DHCA or low-flow CPB (50 mL/kg/min) as the predominant strategy. Alpha-stat management was used, and hematocrits were maintained at about 20%. The main immediate postoperative findings were a higher risk of clinical seizures (odds ratio 11.4), EEG seizures (odds ratio 2.5), longer recovery time to EEG reappearance, and higher creatine kinase brain isoform levels [54]. A total of 155 of these infants were tested at age 12 months with the Bayley Scales of Infant Development-I (Bayley-I), MDI (105.1 ± 15.0) (normal 100, SD ± 15), and PDI (95.1 ± 15.5). The use of DHCA was associated with a 6.5-point deficit on the MDI, and PDI was inversely proportional to the duration of DHCA [170]. EEG seizures were associated with lower PDI scores. At age 8 years, when multiple domains are testable, the 155 returning subjects had overall scores on the Wechsler Intelligence Scale for Children-III as follows: FSIQ, 97.1 ± 15.3; performance IQ, 94.9 ± 14.3; and verbal IQ, 99.8 ± 16.6. The presence of a VSD

was associated with lower verbal IQ scores. Academic achievement scores were generally in the normal range, although 37% were receiving remedial academic services and 10% had repeated a grade [6]. Performance on these tests was decreased when DHCA duration was >41 minutes (95% lower confidence limit, 32 minutes). The cohort as a whole was below expectations in terms of academic achievement, fine motor function, visual–spatial skills, working memory, attention, and higher order language skills. Of these subjects, 139 returned at age 16 years for further neuropsychological testing and brain MRI [71]; 65% of these adolescents utilized some form of specialized educational services, and most scores of academic achievement, memory, executive functions, visual–spatial skills, attention, and social cognition tests were all below reference population norms, mostly in the mid-90th percentile, with no association with DHCA vs. low-flow bypass group. Multivariable analysis revealed associations of parental IQ, DHCA duration, and EEG seizures with one or more neuropsychiatric outcomes. Structural MRI abnormalities, mostly evidence of remote ischemic hemorrhage, were present in 33% of the 111 subjects scanned. On quantitative MRI imaging, the arterial switch operation group as a whole demonstrated reduced fractional anisotropy in bilateral cerebral hemispheric, brainstem, and cerebellar white matter, signifying impaired microstructural development. Shorter cooling duration, higher nadir temperature, longer total ICU length of stay, and need for subsequent operations were all associated with impaired white matter development [171].

The wealth of information gleaned from the BCAS data set the standard for all subsequent single-center studies. The uniform patient group (all D-TGA, no genetic abnormalities) receiving a single corrective surgery is important for minimizing subsequent confounders. The prospective, randomized controlled intervention design, EEG, MRI, and careful serial neurodevelopmental outcomes in a large group with a high follow-up rate are unparalleled thus far in subsequent studies. BCAS also raises the issue that bypass management (i.e., alpha-stat management, rapid cooling, prolonged DHCA, hematocrit 20%) has changed significantly in many centers since the cases were done, and the long-term findings may not be the same with contemporary approaches. The infant outcome tests (e.g., Bayley Scales of Infant Development) have undergone revision and are now in their third version; there is no reliable method to translate results between versions.

Children's hospital of Philadelphia cohort

Gaynor and colleagues enrolled 550 neonates and infants <6 months of age undergoing complex CHD surgery from 1998 to 2003 in a prospective study of apolipoprotein E (APOE) genotype and neurodevelopmental outcomes [172]. APOE is important in neuronal repair and previously had been demonstrated to affect outcome in Alzheimer's disease. This cohort has yielded important information about not only APOE but also a number of other risk factors for impaired neurodevelopmental outcomes through school age. A variety of cardiac diagnoses were enrolled, including a substantial group of HLHS patients. In all 359 subjects tested at 1 year, MDI on the Bayley-II was 90 ± 15, and PDI was 78 ± 18 [173]. The APOE $\varepsilon 2$ allele was associated with significantly lower MDI and PDI scores after multivariable adjustment. Other risk factors were lower birth weight, preoperative intubation, lower hematocrit on CPB, longer postoperative length of stay, additional CPB operations, and genetic syndromes including chromosome 22q11.2 deletion syndromes. The use of DHCA was not associated with lower Bayley-II scores. At age 4 years, neurodevelopmental outcomes were tested in 381 subjects using a battery of standard tests; overall scores in the eight domains tested were within normal ranges; however, more patients had severe impairment in at least one domain than the general population. Cardiac diagnosis was demonstrated to be associated with outcomes, with HLHS patients performing worse than TGA, tetralogy of Fallot, or VSD patients without chromosomal anomalies in unadjusted analyses; these differences were less apparent after multivariable adjustment. In a separate report, EEG seizures in the perioperative period, which occurred in 11% of the cohort, were associated with worse executive function and impaired social interactions [174]. In another report of 92 of these infants who underwent DHCA, with a median of 36 minutes (range 1–132), DHCA was not associated with worse neurodevelopmental outcomes compared with those infants who had not undergone DHCA [175]. Finally, younger gestational age in this cohort was associated with worse outcomes, with 39–40 weeks' gestational age at birth performing better in multiple domains at age 4 years than those born at less than 39 weeks [176]. In a very important and novel report from this cohort, 21.6% of patients had hearing loss at age 4 years, an incidence 20-fold higher than expected in a normal population [177]. Hearing loss was associated with younger gestational age, genetic syndromes, and longer duration of hospital stay. The presence of hearing loss was associated with worse cognition, language, and attention. Possible causative factors included environmental noise in the ICU and ototoxic medications such as furosemide.

Western Canadian study

The Western Canadian Complex Pediatric Therapies Follow-up Group started prospective data collection of neonates and infants <6 weeks of age undergoing complex cardiac surgery in 1996–1999; this group has reported additional cohorts having surgery as late as 2003–2006. A variety of cardiac diagnoses were enrolled, including about one-third with HLHS and one-third with D-TGA. Their initial report of 85 infants included 67 survivors assessed at age 18–24 months with the Bayley-II [178]. The entire cohort has mean MDI of 84 ± 17 and PDI of 80 ± 22; chromosome anomaly conferred a major risk factor and was found in 10 of 67 patients, with mean MDI of 67 ± 16 and PDI of 61 ± 17. Twenty-two percent of the population had profound mental delay (MDI < 70), and 30% profound motor delay (PDI < 70). Associated factors in the multivariable analysis included duration of preoperative ventilation, chromosome anomaly, duration of DHCA and CPB, and low arterial pH and high serum lactate, all associated with significant delay on Bayley-II. This group also assessed 16 subjects with deletion of chromosome 22q11.2 (DiGeorge syndrome), matched for cardiac lesion, socioeconomic status, and year of operation, with 16 patients without 22q11.2 deletion [179]. The 22q11.2 deletion patients (six interrupted aortic arch, six truncus arteriosus, four tetralogy

of Fallot) had lower MDI (66.1 ± 10.6 vs. 86.3 ± 14.6, $P < 0.001$) and PDI (55.5 ± 9.4 vs. 82.3 ± 14.3, $P < 0.001$). In a separate report of this cohort in 61 patients at age 5 years, FSIQ was 89 ± 20, verbal IQ was 90 ± 20, performance IQ was 90 ± 20, and visual motor integration (VMI) was 87 ± 17 [180]. The MDI as assessed at 18–24 months strongly predicted the FSIQ at 5 years ($r = 0.817$).

The Western Canadian Group has also reported on a later cohort, with complex cardiac surgery <6 weeks of age from 2003 to 2006, associating sedative, anesthetic, and analgesic drug exposure and neurodevelopmental outcomes [165, 166]. They calculated the cumulative dose during the first 6 weeks of life for volatile anesthetics, opioids, benzodiazepines, ketamine, and chloral hydrate. At age 18–24 months, they administered Bayley-II or Bayley-III (Bayley-III after July 2004), and adaptive behavior and language were also assessed by parent questionnaire. Multivariable analysis with the drug exposure variables, as well as a number of patient and surgical variables, was performed, with primary outcome being significant mental or motor delay <70 on the Bayley scales, vocabulary delay <15th percentile, and adaptive behavior scores. In all, 135 subjects were enrolled in the study; 19 died, 16 had chromosomal anomalies, and five were lost to follow-up, leaving 95 with neurodevelopmental assessments. Forty-eight percent of patients were D-TGA having undergone arterial switch, 24% were HLHS patients, and the remainder were other 2V complete repairs. The overall cohort had mental and motor scores below the population norms but within 1 SD of normals; 11% had mental delay and 7% motor delay (in the normal population this is 2.5%), while 31% had vocabulary delay (normal is 15%). All patients received volatile agents, benzodiazepines (median 16 days), and opioids (median 15 days); 73% received chloral hydrate, and 56% received ketamine. There was no association with anesthetic or sedative drug dose and profound delays. Increasing days of ventilation, older age at surgery, lowest PaO_2, use of DHCA, and lower maternal education were all associated with significant delays.

Hearts and minds study

The Heart and Minds Study is a prospective longitudinal cohort study of infants <8 weeks of age undergoing cardiac surgery with or without CPB between 2005 and 2008 in Australia and New Zealand [22]. Subjects had preoperative and postoperative brain MRI, and there was data collection and 2-year neurodevelopmental outcome testing using the Bayley-III. About half of the patients were SV palliations, and half were complete 2V repairs. The overall neurodevelopmental scores of the 122 subjects with follow-up at age 2 years were as follows: cognitive, 94 ± 15; language, 94 ± 16; motor, 97 ± 12. The primary aim of the study was to determine the association of WMI with patient and surgical characteristics, and neurodevelopmental outcome. There was no association of WMI with Bayley-III scores; however, structural brain immaturity on MRI was associated with lower neurodevelopment.

Milwaukee cohort

Hoffman and colleagues reported on a cohort of HLHS patients undergoing stage I palliation in 2002–2005, and then neurodevelopmental assessment at age 4–5 years [181]. The primary aim of the study was to determine the association of perioperative regional cerebral oxygen saturation (rSO_2), measured by NIRS, with neurodevelopmental outcomes. Of 51 patients entering the study, 21 had complete neurodevelopmental assessment (48% of survivors). The composite neurodevelopmental outcome of cognition, language, attention, and VMI was 97.6 ± 9.6, was within normal population ranges, and with low performance frequencies also not different from reference population ranges. Patients demonstrating low or abnormal VMI had lower rSO_2 (63.6 ± 8.1 vs. 67.8 ± 8.1, $P = 0.026$) in the first 48 postoperative hours. They also spent more time at $rSO_2 < 55$ and 45% levels than those with normal VMI. Peripheral oxygen saturation (SaO_2) was also lower in these patients; however, other physiological variables (mean arterial pressure,41, SvO_2, central venous pressure, hemoglobin, blood gas parameters) were not different. The breakpoint for lower VMI score in the multivariate model was an rSO_2 of 55%. This team also reported 178 children from their institution followed for 36 months with the BSID-III performed at 6-month intervals after neonatal surgery. At 6 months, SV and 2V patients had Cognitive and Language scores in the normal range, with means below population norms, and these scores remained relatively constant through 36 months. Motor scores started at 0.5–1 SD below normal at 6 months but increased progressively for both SV and 2V patients and were in the normal range at 36 months. In contrast, patients with a genetic syndrome started 1–2 SD below normal in all three domains at 6 months; their Cognitive and Language scores decreased, and Motor scores were constant. By 36 months, all three means were about 2 SD below population norms [139] (Figure 14.18).

Texas children's hospital cohort

The Texas Children's Hospital cohort of neonates undergoing complex cardiac surgery at less than 30 days of age between 2005 and 2011 has been the subject of several neurodevelopmental outcomes publications [8, 18, 138, 182, 183]. Of 93 subjects entering two separate prospective studies, 59 (71%) survivors underwent 12-month Bayley-III testing; 47% of these patients had HLHS. Cognitive score was 102.1 ± 13.3, language score was 87.8 ± 12.5, and motor score was 89.6 ± 14.1. The major findings in these reports after multivariable analyses were as follows:

- Longer duration of regional cerebral perfusion was not associated with lower Bayley-III scores, but longer DHCA was associated with lower scores.
- New postoperative MRI brain injury, longer ICU length of stay, lower preoperative rSO_2, and chromosome anomalies were associated with lower Bayley-III scores.
- Larger volatile anesthetic agent exposure was associated with lower cognitive scores.

By age 36 months, Bayley-III testing of this cohort revealed Cognitive, Language, and Motor score means within normal ranges, with SV patient means for Motor still normal but about 5 points lower. By 5 years, on a full battery of tests, the mean IQ, language, and behavior scores were in the normal range; motor skills for SV patients were about 2/3 SD below normal means, and VMI about ½ SD below normal means [183].

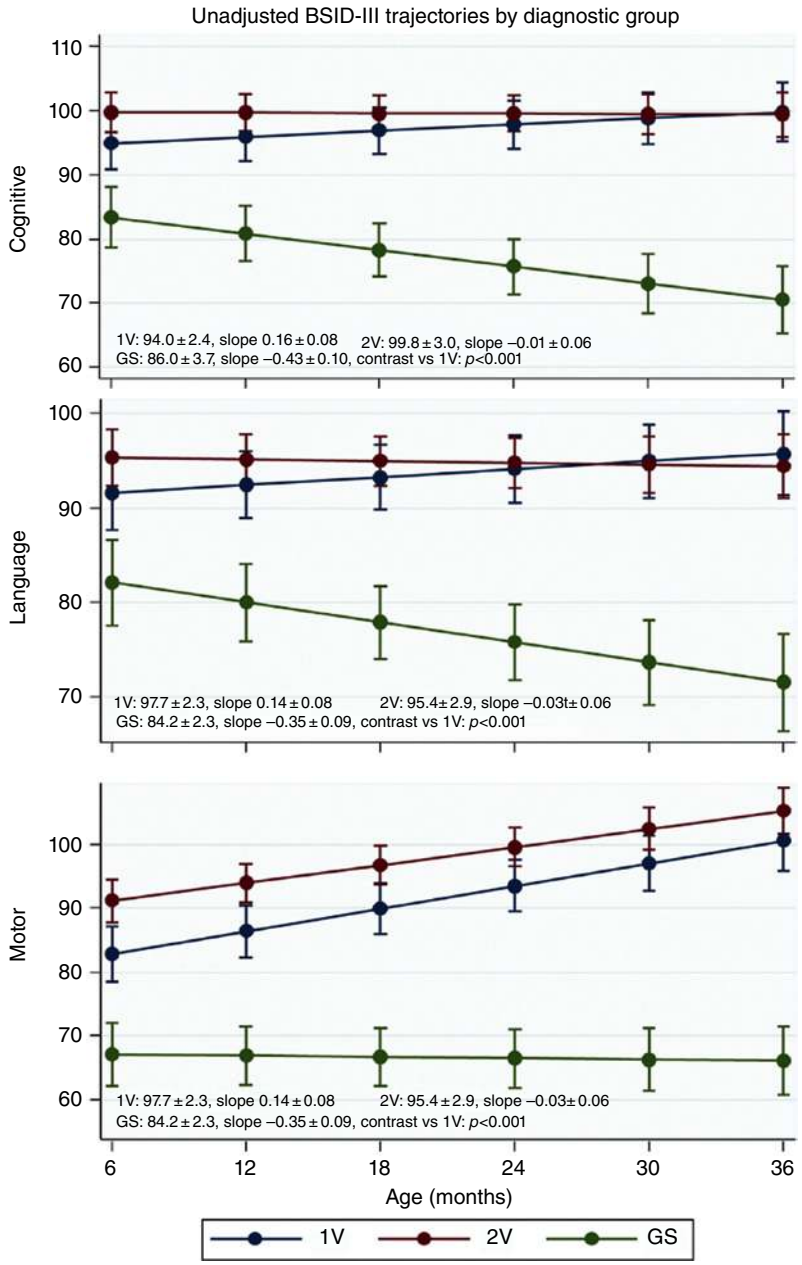


Figure 14.18 Change in Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) score over time by patient diagnostic category of 1 ventricle (1V, blue), two-ventricles (2V, red), and genetic syndrome (GS, green). The linear mixed-effect model parameter estimates and 95% confidence intervals are shown as symbols and range bars. (Source: Hoffman et al. [139]. Reproduced with permission from Elsevier.)

Single ventricle reconstruction trial

The Single Ventricle Reconstruction (SVR) Trial is a multicenter study of stage I palliation for HLHS randomizing surgery to systemic to pulmonary artery shunt vs. right ventricle to pulmonary artery shunt [184]. Operations were performed between 2005 and 2008 in 15 centers. Neurodevelopmental outcomes were assessed with the Bayley-II at a mean of 14.3 ± 1.1 months of age. In all, 314 patients were assessed at that time (86% of transplant-free survivors), and mean MDI was 89 ± 18 and PDI was 74 ± 19, both profoundly lower than reference population norms. Multivariable regression models determined that site of surgery, birth weight less than 2,500 g, longer length of stage I hospitalization, and greater number of complications were associated with lower PDI scores. Lower MDI scores were associated with lower birth weight, genetic syndrome or other anomalies, lower maternal education level, longer days on ventilation, and greater number of complications. Intraoperative variable data collection was limited, but none of these variables (DHCA vs. regional cerebral perfusion, alpha-stat vs. pH-stat, hematocrit) were associated with Bayley-II outcomes. By age 3 years,

mean scores for each domain on a parental questionnaire of neurodevelopment were significantly lower than those of the normal control population. The percentage of children with delayed scores (>2 SD below the mean) was 20% for the Communication Scale, 30% for the Gross Motor Scale, 35% for the Fine Motor Scale, 24% for the Problem Solving Scale, and 17% for the Personal-Social Scale (about 2% would be expected in a normal population). Delay was detected in at least one area for 51% of the cohort [185].

An assessment of behavioral outcomes at 6 years in the SVR cohort reported approximately three times higher risk of impaired adaptive behavior skills and that lower socioeconomic status was associated with lower fine motor, problem-solving, adaptive behavior, communication, and functional status [186, 187]. It should be noted that of 555 subjects entered into the SVR trial, 41% had died by age 6 years, and another 4% required cardiac transplantation; emphasizing the high-risk nature of this patient population for ongoing threats to normal neurodevelopment. Type of shunt does not appear to have any effect on any long-term clinical or neurodevelopmental outcome.

International cardiac collaborative on neurodevelopment (ICCON) investigators cohort

The ICCON Investigators group was recently formed and has pooled early neurodevelopmental outcomes results for complex neonatal and young infancy cardiac surgery with operations occurring between 1996 and 2009 [188]. Data were analyzed from 23 institutions utilizing Bayley-II testing performed on patients aged 6–30 months. The mean age of assessment was 14.5±3.7 months, and the overall scores for the 1,770 patients were MDI 88.2±16.7 and PDI 77.6±18.8. Important findings were that cardiac class IV (SV patients with aortic arch obstruction, e.g., HLHS) was significantly more common in the later years of the studies. In the multivariable analysis, patient factors were evaluated, and cardiac diagnosis (class IV), genetic anomaly, lower maternal education, male gender, and lower birth weight were all associated with lower scores. After this adjustment, mean Bayley-II scores did increase significantly over time, with mean MDI and PDI scores increasing by approximately 0.4 points/year over the 14 years represented in the study (Figure 14.19). Longer total support time (CPB, DHCA, and SCP), use of ECMO, need for cardiopulmonary resuscitation (CPR), and longer duration of ICU stay were all associated with lower MDI and PDI scores.

Zurich cohort

Latal and colleagues describe a single-center cohort of 233 patients undergoing SV and 2V surgery with bypass at median age 3–4 months, who had neurodevelopmental assessments at age 6 years [189]. Of these, 64 (27%) patients had a recognizable genetic syndrome, including trisomy 21, microdeletion of chromosome 22q11.2, VACTERL association, CHARGE syndrome, and others. Median total IQ for nongenetic disorder group was 95 (range 47–135), and

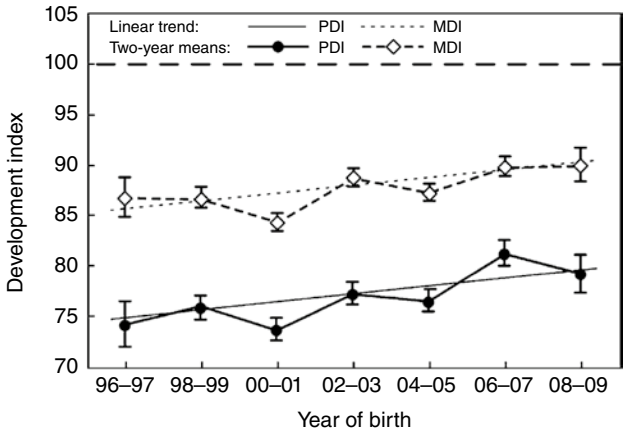


Figure 14.19 Standardized Psychomotor Development Index (PDI) and the Mental Development Index (MDI) using the Bayley Scales of Infant Development, 2nd Edition, from the ICCON Study. Means are displayed by year of birth category. The standardized means plot predicted PDI and MDI and standard error bars based on a model with year of birth category adjusting for center, patient and preoperative factors, operative management factors, and postoperative events at the mean value of the covariates. Overlaid are standardized means plots based on continuous year of birth. The dotted line represents the normative mean of 100 for both PDI and MDI. (Source: Gaynor et al. [188]. Reproduced with permission from Elsevier.)

for the genetic disorder group was 55 (range 17–115), $p < 0.01$. Median scores on tests of language, reasoning, processing speed, and number recall were in the normal range for nongenetic syndrome patients, and 0.6–1.2 SD below norms for the genetic syndrome patients, with all findings significantly different. In multivariable analysis, genetic syndrome, longer ICU stay, lower birth weight, postoperative seizures, and lower socioeconomic status were associated with poor neurodevelopmental outcomes.

The studies reviewed in this section give an emerging, if incomplete, picture of risk factors for the now very well-established lower neurodevelopmental outcomes in infants undergoing congenital heart surgery. Many recent reports emphasize significantly lower testing scores during infancy in most all cohorts; however, there are now more reports at age of school entry or later. These reports at older ages give a profile of the preschool or school-aged child with subtle impairment in a number of domains, including executive functioning, language, attention, fine motor function, VMI, and reasoning. As noted earlier, this profile is not dissimilar to the premature neonate. Both groups have in common structural and microstructural brain immaturity and a propensity to brain injury, with WMI being the most common. Comparison of outcomes over time is difficult because of different testing strategies utilized in different cohorts, [190] but there appears to be a trend of improving early outcomes, albeit in a patient population increasingly skewed toward more complex SV lesions. Debate is ongoing about the proportion of risk accrued to nonmodifiable (i.e., innate) patient factors vs. modifiable ones (i.e., CPB techniques, neurological monitoring, anesthetic and sedative

techniques, and ICU strategies). Interesting new data about association of potentially neurotoxic compounds in the perioperative environment (cyclohexanone, phthalates in plastics) with lower neurodevelopment scores after infant cardiac surgery bears further consideration [191, 192]. Finally, the effect of early childhood intervention and a stimulating home environment has begun to be studied as a means to take advantage of the potential for neuroplasticity in these infants [193, 194].

The multivariable models all have significant limitations, and the majority explain only 20–40% of the variation in the neurodevelopmental outcome scores; only a few models explain >50%. Further complicating the concepts of nonmodifiable factors may be emerging strategies for fetal intervention, by both catheter and medical interventions, that could improve both the cardiac and cerebral abnormalities observed in neonates with CHD. The very strong risk factor that most genetic syndromes confer for adverse neurodevelopmental outcomes is increasingly clear. This becomes more important as cardiac surgery is offered to a broader population of patients with genetic syndromes, i.e., trisomy 13 and 18; and as sophisticated genetic testing (whole exome and genome sequencing) uncovers additional abnormalities associated with neurodevelopmental problems [195]. (See Chapter 8, Genetic Syndromes). Newer approaches to modeling the many complex risk factors include artificial intelligence/machine learning algorithms that may be able to better account for small sample sizes with multiple risk factor variables [196]. Small single-center studies are still the predominant publication type for neurodevelopmental outcomes. The pitfalls of drawing conclusions from multivariable analyses, i.e., frequency of Type I and Type II errors, from small data sets, are evident. Multicenter databases, combined analyses, meta-analyses, and multicenter prospective studies with much larger sample sizes, and standardized outcome measures will be important to move this field forward with higher quality evidence to support beneficial treatment strategies. Table 14.3 summarizes data from the cohorts reviewed earlier, and Table 14.4 presents the modifiable vs. nonmodifiable risk factors published in the studies reviewed here, and lists possible strategies for intervention, where applicable [197, 198].

KEY POINTS: COHORT STUDIES OF NEURODEVELOPMENTAL OUTCOMES

- Most single-center cohort studies demonstrate decrements in motor performance which improves over time.
- Cognitive deficits are less severe, but performance is not normal in most cohorts.
- Language, executive function, and behavior are also not normal in most cohorts.
- Genetic syndromes are a significant risk factor for neurodevelopmental problems.
- Larger patient populations and standardized outcomes are needed to improve data quality.

Conclusions

> Truth in medicine is an unattainable goal, and the art as described in books is far beneath the knowledge of an experienced and thoughtful physician.
>
> Muhammad Ibn Zakariya Al-Razi, *c.* 900 BCE

The neurologic vulnerability of children with CHD has been well characterized. White matter lesions suggestive of impaired oxygen delivery to watershed regions of the brain are the most common perioperative-acquired injury seen on MRI. The neurodevelopmental abnormalities of children with CHD are often subtle disorders of intellect, attention, impulsivity, and executive functioning, which impact the quality of life of survivors of critical heart disease in infancy. The principles of CBF and oxygen delivery are equally well characterized, but the strategies to optimize these parameters during CPB are a subject of vigorous debate. A summary of the advantages and disadvantages of the neuromonitoring modalities discussed in this chapter is given in Table 14.5.

Does a neuroprotective strategy during CPB improve outcome?

Scientific investigation has failed to delineate an evidence-based neuroprotective practice for many of the most basic aspects of care during cardiac surgery and CPB, including the use of circulatory arrest or selective cerebral perfusion, and whether and how to monitor the brain during and after CPB. The perspective presented in this chapter emphasizes the physiologic principles relevant to neuroprotection, which are often the only available rationale for decisions that have to be made for critically ill children with CHD.

Single-center studies of cerebral oximetry where goal-directed therapy with cerebral oximetry monitoring is either embraced or rejected cannot show the effect of these practice shifts for lack of a comparison group. Outcomes from the Texas Children's Hospital for neonates requiring cardiac surgery have been studied for both MRI-detected injury and neurocognitive performance. The CPB strategy at Texas Children's Hospital is highly standardized to the use of goal-directed oxygen delivery support and selective perfusion techniques guided by multimodal neuromonitoring, including both reflectance NIRS and TCD insonation [199]. The rates of new neurologic injuries after surgery with this practice compare favorably with published studies of similar outcome measures. A varied critical lesion infant cohort, including HLHS, TGA, truncus arteriosus, and interrupted aortic arch, demonstrated a 36% new MRI injury rate, with only 16% showing new WMI (see Figure 14.2 for comparison data) [17]. For the highest -risk neonates requiring arch reconstruction, the duration of CPB and duration of selective perfusion were both free from association with low 12-month developmental score in any of the three domains tested: cognitive, motor, and language. The duration of circulatory arrest was, however, significantly associated with decreased cognitive performance at 12 months [8]. Thus, the goal-directed strategy, utilizing neuromonitoring, is a safe option for the management of CPB in neonates, but has not been shown to be superior to either circulatory arrest or nonmonitored management in a randomized setting.

Table 14.3 Summary of major neurodevelopmental outcomes Cohorts after complex infant cardiac surgery

Cohort (references)	N	Single (S) or multi-center (M)	Years of surgery	Age at follow-up	ND outcomes	Major associations
Boston circulatory arrest study [6, 54, 71, 170, 171]	155	S	1988–1992	1, 8, 16 years	MDI 105, PDI 95 (1); FSIQ 97, PIQ 95, VIQ 100; adolescents with most scores mid-90th percentile	Prolonged DHCA with outcomes at 1 and 4 years; parental IQ, DHCA duration, EEG seizures at 16 years
Philadelphia APOE study [172–177]	381	S	1998–2003	1, 4 years	MDI 90, PDI 78; 92–105 on 8 domains at 4 years, mean 97	APOE ε2 allele; lower BW, pre-op intubation, lower CPB hct, LOS, additional CPB operations, chromosome/genetic anomaly, EEG seizures, younger GA, cardiac diagnosis (HLHS), hearing loss; DHCA use not associated
Western Canadian Outcomes Group I [178–180]	61	S	1996–1999	18–24 months, 4–5 years	MDI 84, PDI 80; FSIQ 89, VIQ 90, PIQ 90, VMI 87	Chromosome anomaly, pre-op ventilation, duration of DHCA and CPB, acidosis, lactate
Western Canadian Outcomes Group II [165, 166]	95	S	2003–2006	18–24 months, 4–5 years	MDI 86, Cog 98; PDI 85, Motor 95	Days of ventilation, older age, low PaO_2, use of DHCA, lower parental education; days of chloral hydrate, cumulative dose benzodiazepines
Hearts and minds study [22]	122	M (2)	2005–2008	2 years	Cog 94, Lang 94, Motor 97	Brain immaturity
Milwaukee HLHS cohort [181]	21	S	2002–2005	4–5 years	Cognitive IQ 95, attention 107, language 95, VMI 93	rSO_2, SaO_2
Milwaukee cohort II-SV, 2V, genetic syndromes [139]	178	S	2007–2012	6–36 months	36 months outcomes: SV/2V Cog 100, Lang 94–95, Motor 100–105; Genetic Syndrome: Cog 70, Lang 72, Motor 67	rSO_2
Texas children's hospital cohort [8, 18, 151, 182, 183]	59	S	2005–2011	12 months, 36 months, 5 years	12 months: Cog 102, Lang 88, Motor 90; 36 months: Cog 97, Lang 95, Motor 98; 5 years: IQ 98, Lang 98, Motor 94, behavior 96	Volatile anesthetic exposure, ICU LOS, chromosome anomaly, MRI brain injury, rSO_2, DHCA; longer RCP not associated
Single ventricle reconstruction trial [184–187]	314	M (15)	2005–2008	14 months, 3 years, 6 years	MDI 89, PDI 74; 3–6 years: 10–15× higher percentage of delayed language, motor, problem-solving, social problems	BW, site of surgery, LOS, complications, chromosome anomaly, parental education, medical complications, SES
International cardiac collaborative on neurodevelopment [188]	1,770	M(23)	1996–2009	6–30 months	MDI 88, PDI 78	Later year of surgery, cardiac class, genetic anomaly, lower BW, parental education
Zurich cohort [189]	233	S	2004–2009	5–7 years	IQ 95 nongenetic, 55 genetic; Verbal, language, reasoning, processing speed: 93–103 nongenetic, 96–91 genetic	Longer ICU LOS, lower BW, seizures, lower SES

MDI, Bayley Scales of Infant Development-II Mental Development Index; PDI, Bayley Scales of Infant Development-II Psychomotor Development Index; Cog, Lang, Motor, Bayley Scales of Infant Development-III cognitive, language, and motor composite scores. (1) BCAS used Bayley-I. ICU, intensive care unit; LOS, length of stay: MRI, magnetic resonance imaging; EEG, electroencephalogram; rSO_2, regional cerebral oxygen saturation; BW, birthweight; GA, gestational age; VMI, visual motor integration; FSIQ, full-scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; SES, socioeconomic status.

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Table 14.4 Modifiable and Nonmodifiable Published Risk Factors for Lower Neurodevelopmental Outcome Scores after Infant Congenital Heart Surgery

Nonmodifiable Factors	Factor (Example)	Potential interventions
	Cardiac diagnosis (HLHS)	??Fetal catheter intervention; maternal O_2 administration
	Genetic anomaly (22q11.2)	
	Parental education/SES	
	Birthweight	
	Prematurity	
	Brain immaturity	??Maternal progesterone [197, 198]
	Gender	
Modifiable factors		
	Use and duration of DHCA	Avoid/limit DHCA duration [6]
	Use of RCP	Use RCP in lieu of DHCA [199]
	CPB hematocrit	Maintain >24% [46]
	Low rSO_2	Intervene <50%
	MRI brain injury	Avoid/limit DHCA duration [22]
	Elective delivery <39 weeks GA	Avoid [176]
	ICU LOS	Early extubation; minimize sedation [182]
	Seizures	Benzodiazepines [111]
	Anesthetic technique	Limit volatile anesthetic exposure, ??dexmedetomidine [182]
	Low cardiac output/acidosis/lactate	Surgical, anesthetic, ICU strategies
	Low PaO_2	Oxygen delivery strategies; early surgical intervention

Nonmodifiable factors could potentially be modifiable; experimental interventions are listed. HLHS, hypoplastic left heart syndrome; 22q11.2, partial deletion chromosome 22; SES, socioeconomic status; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; rSO_2, regional cerebral oxygen saturation; MRI, magnetic resonance imaging; GA, gestational age; ICU, intensive care unit; LOS, length of stay.

Table 14.5 Practical advantages and disadvantages of specific neuromonitoring modalities

Monitor	Advantages	Disadvantages
Electroencephalograph	Detects subclinical seizures and confirms electrical silence during deep hypothermia.	Requires expertise for interpretation; cumbersome array of electrodes.
Transcranial Doppler	Allows for assessment of cerebral blood flow (velocity) during critical stages of cardiopulmonary bypass, especially selective perfusion.	Technically challenging; flow velocities are dependent on the angle of insonation, which can be difficult to stabilize.
Jugular venous oximetry	Gold standard measurement of cerebral venous oxygen content.	Requires expertise to place the catheter in the jugular bulb; invasive to the cephalad venous drainage system in pre-Glenn patients.
Near-infrared spectroscopy (NIRS)	Noninvasive measure of cortical blood oxygenation; technically easy to apply with a stable signal. Most widely used and familiar neuromonitor in the cardiac patient.	Practical limitations are rare; disposable sensors are costly. Most centers that do not use reflectance NIRS do so for lack of level III outcome evidence.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

6 Bellinger DC, Wypij D, duPlessis AJ, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1385–96. The 8-year follow-up study of neonates undergoing circulatory arrest or low-flow bypass for arterial switch operation. Cutoff for lower neurodevelopmental scores is 41 minutes of circulatory arrest.

16 Mahle WT, Tavani F, Zimmerman RA, et al. An MRI study of neurological injury before and after congenital heart surgery. Circulation 2002;106:I109–14. First neonatal MRI study before and after cardiac surgery, demonstrating a high incidence of WMI present even before surgery, with a significant incidence of new injury after surgery.

21 Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. N Engl J Med 2007;357:1928–38. A landmark study documenting abnormal microstructural brain development in neonates with congenital heart disease.

31 Greeley WJ, Kern FH, Ungerleider RM, et al. The effect of hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral metabolism in neonates, infants, and children. J Thorac Cardiovasc Surg 1991;101:783–94. One of a series of classic studies laying the foundation for modern understanding of cerebral physiology during and after cardiopulmonary bypass.

39 Smith B, Vu E, Kibler K, et al. Does hypothermia impair cerebrovascular autoregulation in neonates during cardiopulmonary bypass? Paediatr Anaesth. 2017;27:905–10. A study of cerebral pressure autoregulation utilizing the hemoglobin volume index in 72 neonates undergoing surgery with bypass and assessed this parameter at different levels of hypothermia down to 18 °C. The lower mean arterial pressure limit of autoregulation ranged from 25 to 45 mmHg, with a trend upward in the first month of life. Demonstrated that this noninvasive NIRS-based method has the potential to monitor autoregulation in real time.

46 Wypij D, Jonas RA, Bellinger DC, et al. The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: results from the combined Boston hematocrit trials. J Thorac Cardiovasc Surg 2008;135:355–60. An important randomized controlled trial demonstrating that extreme hemodilution on bypass is associated with lower neurodevelopmental outcome status at age 12 months.

80 Andropoulos DB, Stayer SA, McKenzie ED, Fraser CD Jr., Novel cerebral physiologic monitoring to guide low-flow cerebral perfusion during neonatal aortic arch reconstruction. J Thorac Cardiovasc Surg 2003;125:491–9. A study describing the technique of transcranial Doppler monitoring of cerebral blood flow velocity during selective cerebral perfusion to ensure adequate but not excessive cerebral blood flow when adjusting bypass flow rate during this technique.

100 Austin EH 3rd, Edmonds HL Jr, Auden SM, et al. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. J Thorac Cardiovasc Surg 1997;114:707–17. Retrospective study in 250 neonates, infants, and children undergoing cardiac surgery demonstrating the ability of multimodality neuromonitoring to reduce acute neurological injury. Near-infrared spectroscopy was the most important monitor.

116 Alkhatip AAAMM, Kamel MG, Farag EM, et al. Deep hypothermic circulatory arrest in the pediatric population undergoing cardiac surgery with electroencephalography monitoring: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2021: Online ahead of print. A systematic review and meta-analysis of 19 studies and 1267 pediatric patients undergoing cardiac surgery with DHCA and EEG monitoring. The event rate for EEG seizures was 14.9%; and seizures were associated with acute neurological findings, MRI abnormalities, and lower IQ and PDI scores on long-term follow-up. Longer DHCA times were associated with a higher incidence of EEG seizures.

137 Carra G, Flechet M, Jacobs A, et al. Postoperative cerebral oxygen saturation in children after congenital cardiac surgery and long-term total intelligence quotient: a prospective observational study. Crit Care Med. 2021. Online ahead of print. A study of 87 infants with median age 4 months undergoing cardiac surgery with bypass and found that higher "dose" of cerebral desaturation below rSO_2 of 65% (% below 65% × minutes) in the first 24 hours after surgery was associated with lower IQ scores 2 years later.

139 Hoffman GM, Brosig CL, Bear LM, et al. Effect of intercurrent operation and cerebral oxygenation on developmental trajectory in congenital heart disease. Ann Thorac Surg 2016;101:708–16. A study of 178 children followed for 36 months with the Bayley Scales-III performed at 6-month intervals after neonatal surgery. At 6 months, SV and 2V patients had Cognitive and Language scores in the normal range, with means below population norms, and these scores remained relatively constant through 36 months. Motor scores started at 0.5–1 SD below normal at 6 months but increased progressively for both SV and 2V patients and were in the normal range at 36 months. In contrast, patients with a genetic syndrome started 1–2 SD below normal in all three domains at 6 months; Cognitive and Language scores decreased, and Motor scores were constant; by 36 months, all three means were about 2 SD below population norms. Lower baseline rSO_2, but not pulse oximeter-derived SpO_2, measured at the time of neurodevelopmental assessment, was a risk factor for lower motor scores from 6 to 36 months of age.

146 Ferradal SL, Yuki K, Vyas R, et al. Non-invasive assessment of cerebral blood flow and oxygen metabolism in neonates during hypothermic cardiopulmonary bypass: feasibility and clinical implications. Sci Rep 2017;7:44117. A small study of frequency-domain NIRS/DCS demonstrating that this noninvasive method measures the uncoupling of cerebral blood flow and $CMRO_2$ during deep hypothermia, with closely similar results to the invasive methods used by Greeley and colleagues more than 30 years previously.

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CHAPTER 15

Transesophageal and Epicardial Echocardiography in Congenital Heart Disease

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Introduction

Currently, most institutions use a combination of imaging modalities, including echocardiography, cardiac catheterization and angiography, computed tomography (CT), and cardiac magnetic resonance (CMR), for the comprehensive diagnostic evaluation of patients with congenital heart disease (CHD). Transesophageal echocardiography (TEE) has evolved over time to become a critically important cardiovascular imaging modality that has major benefits, particularly in the perioperative setting.

Since the introduction of TEE in the late 1980s, it has proven useful as a diagnostic and monitoring tool in adult patients during cardiac and noncardiac surgery. Until the early 1990s, intraoperative TEE in infants and small children was not feasible, as TEE probes of a suitable size were unavailable. Advances in ultrasonography technology, specifically the miniaturization of imaging probes, have since permitted the safe use of TEE in these patients.

Most cardiac centers currently consider TEE to be the standard of care for assessing the adequacy of surgical interventions in children and adults with CHD. This imaging approach can immediately detect suboptimal surgical results, thus improving clinical outcomes by avoiding subsequent reoperations and reducing overall morbidity, mortality, and costs. The use of TEE in environments such as the cardiac catheterization laboratory, electrophysiology suite, and intensive care unit (ICU) also significantly facilitates the management of patients with CHD. Although TEE is not commonly used for purely diagnostic indications in children, many adults with CHD and challenging images benefit significantly from this use of TEE.

Epicardial echocardiography (E-echo), which directly places the probe on the heart surface, provides an option to image the heart when TEE is unavailable or contraindicated, or when this modality can provide information that complements the TEE findings in the operating room or ICU.

This chapter focuses on the use of TEE and E-echo for monitoring and assessment in CHD patients, highlighting these modalities' many benefits and roles in clinical practice. The emphasis is on intraoperative use, as this is the most common application of the technology in CHD patients.

Indications for TEE in CHD

Echocardiography is the preferred imaging modality for the initial diagnostic assessment and serial follow-up of patients with CHD. Transthoracic echocardiography

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(TTE) provides excellent definition of cardiovascular anatomy in most patients. In fact, the exceptionally high resolution of TTE imaging in infants and young children with CHD is often sufficient to plan medical and surgical management. Published standards exist for the echocardiographic assessment of pediatric and adult patients with CHD, including TTE, TEE, quantification, and 3D imaging [1–5].

Despite the merits of TTE, its technical limitations result in suboptimal imaging in patients with poor windows caused by obesity, mechanical ventilation, and prior or recent cardiac surgery. TEE overcomes many of these limitations and can be extremely helpful when other imaging approaches, including TTE, provide insufficient information or there is a need to answer important diagnostic questions. The portability of TEE makes it easy to perform in various settings. TEE in the patient with CHD is often an adjunct to other diagnostic studies and, as such, should complement, but not substitute for, a complete TTE examination.

Several professional societies in North America and other countries have proposed indications for the use of TEE [3, 6–9]. Guidelines published by the American Society of Echocardiography (ASE) in 2005 and 2019 address specific indications for TEE in pediatric patients and in all patients with CHD [5, 10]. These documents describe three major categories of indications for TEE in CHD patients: diagnostic assessment, perioperative evaluation, and related to percutaneous interventions (Table 15.1).

Outpatient TEE is a routine diagnostic tool used in many centers that care for adult patients with cardiovascular disease, including CHD, because transthoracic imaging becomes more challenging and less revealing as patients reach adulthood [11]. The TEE modality plays an important role in this setting, as congenital anomalies are highly variable in presentation. The benefits of TEE include the detailed evaluation of primary structural malformations, secondary compensatory cardiovascular changes, associated complications, and functional and hemodynamic consequences. The proximity of the imaging probe to the back of the heart provides optimal visualization of cardiovascular structures. Overall, TEE is superior to TTE for diagnosing specific pathologies involving the aorta (Ao) and left atrial appendage (LAA) and for evaluating prosthetic heart valves, native valve masses, and complications resulting from endocarditis, including vegetations, abscesses, and fistulae [3]. It is the imaging approach of choice to exclude thrombus before performing elective cardioversion in most patients with atrial rhythm disturbances. The TEE imaging approach is also useful in evaluating potential cardiac sources of embolism, such as a patent foramen ovale (PFO) [12]. The modality can also enhance the assessment of intracardiac or extracardiac baffles in patients who have undergone Fontan, Senning, or Mustard procedures [13, 14].

Intraoperative evaluation represents a frequent application of TEE and has the following goals [15]:

- Confirm and refine the preoperative diagnosis
- Detect new or unsuspected pathology
- Adjust the anesthetic and surgical plan
- Assess the results of the surgical intervention

Table 15.1 Indications for transesophageal echocardiography (TEE) in the patient with congenital heart disease (CHD)

Diagnostic indications
• Patient with suspected CHD and nondiagnostic transthoracic echocardiography (TTE)
• Presence of patent foramen ovale (PFO) with and without agitated saline contrast and direction of shunting as possible etiology for stroke
• Evaluation for cardiovascular source of embolus with no identified noncardiac source
• Evaluation of intracardiac or extracardiac baffles after the Fontan, Senning, or Mustard procedure
• Suspected acute aortic pathology, including, but not limited to, dissection/transection (e.g., Marfan syndrome, bicuspid aortic valve, coarctation of the aorta)
• Intracardiac evaluation for vegetation or suspected abscess
• Evaluation for intracardiac thrombus prior to cardioversion for atrial flutter/fibrillation and/or radiofrequency ablation
• Pericardial effusion or cardiac function evaluation and monitoring postoperative patient with open sternum or poor acoustic windows
• Evaluating status of prosthetic valve in the setting of inadequate TTE images
• Reevaluation of prior TEE finding for interval change (e.g., resolution of thrombus after anticoagulation, resolution of vegetation after antibiotic therapy)
Perioperative indications
• Immediate preoperative definition of cardiac anatomy and function
• Postoperative surgical results and function
• Intraoperative monitoring of ventricular volume and function
• Monitoring of intracardiac/intravascular air and adequacy of cardiac de-airing
TEE-guided interventions
• Guidance for placement of occlusion device (e.g., septal defect, Fontan or intra-atrial baffle fenestration)
• Guidance for blade or balloon atrial septostomy
• Guidance for creation/stenting of interventricular communication
• Guidance during percutaneous valve interventions
• Guidance during radiofrequency ablation procedure
• Assessment of results of minimally invasive surgical incision or video-assisted cardiac procedure
• Guidance during placement of catheter-based cardiac assist device (e.g., Impella heart pump)

Source: Puchalski et al. [5]. Reproduced with permission of Elsevier.

A summary of the indications in both adults and children with CHD includes [5]:

- All open-heart and most thoracic aortic surgical procedures
- Surgical repair of most congenital heart lesions that require cardiopulmonary bypass (CPB)
- Surgery to treat significant residual abnormalities, such as outflow tract obstruction, valve regurgitation or stenosis, or intracardiac communications

TEE may provide significant benefits in patients with CHD undergoing cardiac catheterization procedures, such as device closure of intracardiac communications (atrial septal defects [ASDs] or ventricular septal defects [VSDs]), balloon valvuloplasty, perforation of the atretic pulmonary valve, and atrial septostomy [16–19]. Likewise, TEE can be extremely

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useful during electrophysiologic procedures by guiding catheter placement and assisting with ablation therapies [20, 21]. In these various applications, TEE can offer valuable information that facilitates planning, refinement, and, upon completion of the intervention, real-time assessment of the results.

Despite its considerable merits, TEE has inherent limitations, including the following:

- Imaging constraints within the gastrointestinal tract, resulting, in some cases, in suboptimal evaluation of structures or Doppler angles of interrogation
- Reduced far-field imaging of anterior structures compared with TTE
- Semi-invasiveness, often necessitating sedation or general anesthesia, with associated risks
- Suboptimal examination conditions related to patient or environmental factors, such as limited time to perform a comprehensive study, ambient lighting, and electrocautery interference

KEY POINTS: INDICATIONS FOR TEE

- TTE adequately characterizes congenital cardiovascular malformations in most patients, particularly in children.
- TEE overcomes many of the limitations of TTE imaging, including suboptimal windows caused by obesity, mechanical ventilation, and previous cardiac surgery.
- The main indications for TEE include diagnostic assessment, perioperative evaluation, and guiding percutaneous interventions.
- Perioperative use represents the most common application of TEE in the patient with CHD.
- In the patient with CHD, TEE should complement, not replace, a complete TTE examination.

Contraindications to TEE

Before using transesophageal imaging, it is prudent to carefully consider the indications, exclude contraindications, obtain informed consent, and completely review relevant clinical information, including all available echocardiographic studies and other diagnostic data. Given the potential risks associated with this semi-invasive procedure, the need for TEE requires judicious decision-making for every patient. In any clinical situation in which safety concerns exist, one should consider alternate imaging modalities such as E-echo, discussed later in this chapter.

General contraindications to TEE include esophageal pathology, severe respiratory decompensation, and inadequate control of the airway (Table 15.2) [3, 5]. The risk-to-benefit ratio for TEE warrants cautious assessment in patients with cervical spine injury or deformity and those with severe coagulopathy. The presence of a gastrostomy feeding tube often necessitates deferring the transgastric (TG) and deep transgastric (DTG) examinations. Although there is no established timing for safe esophageal instrumentation after esophageal surgery, anecdotally, many children have undergone TEE imaging several months or years later without notable ill effects.

Table 15.2 Contraindications to transesophageal echocardiography

Absolute
• Unrepaired tracheoesophageal fistula
• Esophageal obstruction or stricture
• Perforated hollow viscus
• Active gastric or esophageal bleeding
• Poor airway control
• Severe respiratory depression
• Uncooperative, unsedated patient
Relative
• History of esophageal or gastric surgery
• History of esophageal cancer
• Esophageal varices or diverticulum
• Recent gastrointestinal bleeding
• Active esophagitis or peptic ulcer disease
• Vascular ring or aortic arch anomaly with or without airway compromise
• Oropharyngeal pathology
• Severe coagulopathy
• Significant thrombocytopenia
• Cervical spine injury or anomaly
• Post-gastrostomy or fundoplication surgery limits imaging to esophageal windows

Source: Puchalski et al. [5]. Reproduced with permission of Elsevier.

KEY POINTS: CONTRAINDICATIONS TO TEE

- TEE is a semi-invasive procedure with associated risks.
- The use of TEE requires considering the indications and contraindications, reviewing all available patient data, and obtaining informed consent.
- One should consider the absolute and relative contraindications for TEE and perform it only after a careful risk–benefit assessment.

TEE hardware

Using echocardiography requires knowing the science of ultrasound and the many important principles involved. The application of TEE assumes a thorough understanding of the instrumentation needed to perform the examination. This chapter cannot address these aspects of echocardiography and TEE practice, even in an abbreviated form; the interested reader is referred to detailed resources on the subject [22–28].

Echocardiographic system

Ultrasonography machines suitable for echocardiography incorporate multiple modalities for image and signal processing during interrogation of the heart and vasculature.

Modern systems integrate components such as a high-resolution display, a console with hard keys, connection ports for transducers, ports for physiologic monitors (e.g., electrocardiogram), and a computer with software for processing data and network ports.

Controls and their layout on the machine vary by manufacturer; nonetheless, some common features among systems merit a basic understanding of their function. By manipulating various knobs, one can adjust image quality, activate different modes, record images, and perform other functions. Understanding how the machine operates is essential for acquiring images of diagnostic quality. Discussions of these important aspects of echocardiography are available in print [25, 26] and in a number of web-based resources.

TEE imaging probes

Several TEE probes are commercially available for clinical use (Table 15.3). In general, probes are not interchangeable among different echocardiographic systems and may not even be compatible between machines across the same platform. Using a TEE probe in a particular system requires not only appropriate hardware compatibility but also specific software to interface the imaging device with the echocardiography machine.

The evolution of transducer technology has produced TEE probes that have higher resolution than the first probes, as well as enhanced image plane options and additional modes to better assess the cardiovascular system. These advances represent major improvements in our ability to evaluate complex disease comprehensively.

Early *monoplane* (single-plane) TEE probes provided imaging only in the transverse orientation or horizontal plane (0°) [29]. *Biplane* probes incorporated a second scanning crystal that enabled, in addition, imaging in the longitudinal orientation or vertical plane (90°), thereby providing information in planes perpendicular to each other (i.e., orthogonal planes) [30–34]. The introduction of *multiplane* (omniplane) probes permitted interrogation of cardiovascular anatomy in any plane between 0° and 180° [35–38]. These flexible devices all contain phased-array transducers that produce "pie-shaped" or sector images. Sophisticated multiplane probes with many imaging planes to visualize most cardiac structures have largely replaced monoplane and biplane devices (Figure 15.1).

Three-dimensional (*3D*) *volume* TEE and TTE scanning involves using a specialized matrix array probe to display a selected volume of the heart as a real-time 3D data set [39]. Manipulating the data in real time can display anatomy from any perspective, including the surgical orientation [40, 41]. This latest advance replaces previously available 3D technology, which relied on off-line reconstruction of sequentially acquired two-dimensional (2D) image planes, thus limiting its use in the operating room.

Device selection

Unlike the almost "one-size-fits-all" approach to selecting a TEE probe in an adult, choosing among available TEE devices adds another layer of complexity and sometimes even inconvenience to imaging pediatric patients (Figure 15.2). Two parameters guide the selection of an appropriate probe in the pediatric age group: patient weight and probe size (Table 15.4).

At this time, it is rare to use monoplane and biplane TEE probes, as these may no longer be serviced by their respective manufacturers. However, several centers worldwide, mainly in countries with limited resources, still perform biplane and even monoplane TEE imaging in infants and children.

The *pediatric multiplane probe* (*mini-multiplane*) has allowed safe TEE imaging for many years in infants and small children weighing more than 3 kg. The availability of an even smaller device, a neonatal *micro-multiplane probe*, allows the use of this imaging modality in tiny neonates weighing as little as 2.5 kg [42]. These TEE probes incorporate full 2D and Doppler capabilities [43]. In clinical practice, the use of both pediatric and neonatal TEE probes occurs in even smaller patients than recommended by the equipment manufacturers [44, 45].

Table 15.3 Currently available multiplane transesophageal echocardiography (TEE) probes for clinical use

TEE device	Tip dimensions (W × H × L, in mm)	Shaft dimensions (W × L, mm × cm)	Number of elements	Imaging frequencies (MHz)
Philips				
Neonatal or micro-multiplane (S8-3t)	7.5 × 5.5 × 18.5	5.2 × 88	32	3.0–8.0
Pediatric or mini-multiplane (S7-3t)	10.7 × 8.0 × 27	7.4 × 70	48	3.0–7.0
Adult 2D multiplane (S7-2t)	15.0 × 12.5 × 35	10.0 × 90	64	2.0–7.0
Adult 3D (X8-2t)	17.0 × 13.4 × 38	10.0 × 100	2,500 matrix	2.0–8.0
Siemens				
Pediatric multiplane (V7M)	10.7 × 8 × 36*	7.0 × 70	48	4.0–8.0
Adult multiplane (V5M)	14.5 × 11.5 × 45	10.5 × 110	64	3.5–7.0
Adult 3D/4D (Z6Ms)	15.0 × 12.0 × 40	10.2 × 100	2,304 matrix	
General Electric				
Neonatal or micro-multiplane (10T-D)	7.6 × 5.6 × 16	5.6 × 90	32	3.3–10.0
Pediatric micro-multiplane (9T, 9Tc, 9T-RS)	10.9 × 8.4 × 35.2	7.0 × 70	48	3.0–10
Adult multiplane (6T, 6Tc, 6Tc-RS))	14.0 × 12.5 × 45	10.5 × 110	64	3.0–8.0
Adult 3D/4D (6VT-D)	14.3 × 12.7 × 44.8	10.5 × 110	2,500 matrix	3.0–8.0

Abbreviations: H height; *L* length; *W* width

Probe specification information provided by respective companies.

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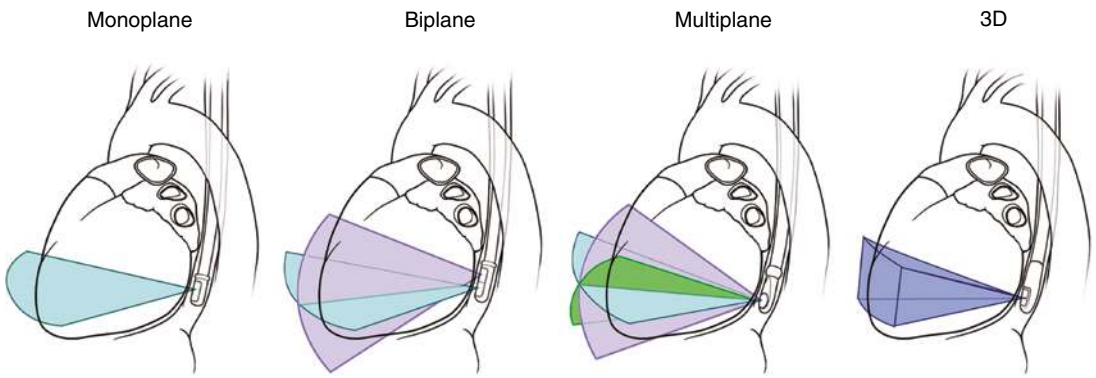


Figure 15.1 *Evolution of TEE imaging hardware*. The graphic displays the evolution of TEE imaging technology from monoplane to biplane, to multiplane, to 3D devices. (Source: Texas Children's Hospital. Reproduced with permission.)

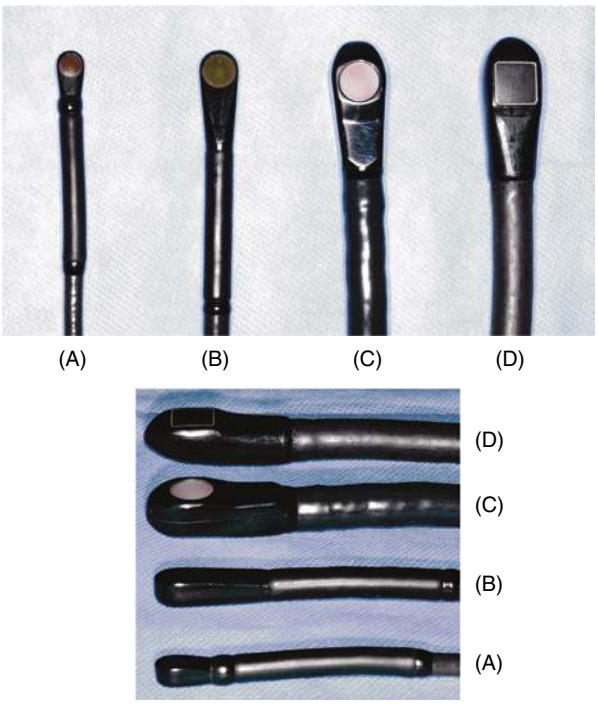


Figure 15.2 *TEE multiplane probes*. The photograph shows four currently available TEE multiplane imaging devices. (A) Neonatal probe; (B) pediatric probe; (C) "adult" 2D probe; (D) "adult" 3D probe.

Table 15.4 Manufacturer recommendations for multiplane transesophageal echocardiography (TEE) probe selection according to patient weight

TEE multiplane probe	Minimum patient weight (kg)
Neonatal	2.5
Pediatric	3.5
Adult (2D)	25
Adult (3D)	30

2D two-dimensional; *3D* three-dimensional

In older children, the preference is to use multiplane imaging with an adult-sized TEE probe, if feasible. Current 3D TEE probes have slightly larger dimensions than available adult 2D TEE probes, rendering them unsuitable for use in most young children. Although manufacturers suggest a patient weighing greater than 25 kg to use an adult 2D TEE probe or greater than 30 kg for a 3D TEE probe, in clinical practice, the usage of these devices often occurs in children weighing less than this. In general, these probes have more piezoelectric crystals than equivalent pediatric devices, and their larger size may improve contact with the esophagus; both features enhance the overall image resolution.

Intracardiac echocardiography (ICE) catheters (8–10 F) inserted via the transesophageal approach can provide 2D imaging in a single, longitudinal plane in neonates and small infants [46–48]. Although these catheters are not formally marketed for this specific application, reports indicate that they deliver clinically useful information in some cases, albeit with several limitations.

Probe insertion

In the operating room, TEE probe insertion occurs after induction of general anesthesia, endotracheal intubation, and arterial catheter placement. Although aspirating gastric contents is standard anesthetic practice in many centers, it does not reliably enhance TEE image quality [49]. In pediatric patients, some providers prefer nasal rather than oral endotracheal intubation to better stabilize the endotracheal tube (ETT), which reduces the risk of inadvertent extubation or movement during TEE probe manipulation. This practice, however, is variable. Regardless of the intubation route, securely taping the ETT should minimize the risk of displacement.

Blind positioning of the lubricated probe tip in the oropharynx with gentle advancement into the esophagus should occur with the patient's head in the midline position. The probe control for transducer tip flexion should remain unlocked at this time to allow free movement.

Slight anterior flexion of the probe tip, forward thrusting of the mandible, and device guidance with a gloved finger can aid advancement of the probe along the contour of the posterior pharynx, thereby minimizing trauma. Alternatively, laryngoscopy can be used initially with direct visualization during probe insertion or after a difficult blind probe insertion [50].

In children, positioning the head to the side may facilitate the probe's passage, as this position reportedly results in closure of the ipsilateral pyriform sinus, where the probe may

encounter obstruction [51]. After placing the transducer behind the heart, repositioning the patient's head avoids interference with the surgical field during probe manipulation. Independent factors that render probe insertion difficult in infants weighing 4 kg or less include lower weight, abnormal craniofacial anatomy, prematurity, a diagnosis of 22q11 deletion [52], and, possibly, Down syndrome.

Probe placement is an essential skill in the practice of TEE. Distinguishing expected from excessive resistance requires thorough expertise and ongoing experience with the technique [53]. Although esophageal intubation requires some degree of effort, it is important never to force the probe against resistance. Manufacturers recommend insertion of the TEE probe through a bite block (also referred to as bite guard), which is positioned between the patient's teeth to provide safe passage through the patient's mouth, prevent damage to the TEE probe, and maintain the probe warranty. In clinical practice, this is more commonly used when imaging is done under sedation than with general anesthesia and more likely to be used in adults versus children.

Probe insertion and manipulation can be significantly stimulating and requires an adequate level of patient sedation or anesthesia and even neuromuscular blockade in most children before placement. These maneuvers can also elicit clinically significant hemodynamic and/or respiratory changes, particularly in patients with specific anomalies with known significant potential risks of TEE (e.g., anomalous pulmonary venous drainage, vascular rings or slings); thus, vigilance is imperative [54]. In the event of acute hemodynamic or airway compromise, the probe should be repositioned or removed immediately.

Outpatient TEE is performed often in adults but rarely in children, because the excellent image quality of TTE in the pediatric population provides adequate information as previously noted. In most cases, TEE is used to address a specific question, such as assessing for a thrombus in the LAA. A combination of oropharyngeal topical anesthesia and intravenous sedation may be sufficient for TEE imaging in the adolescent or adult. In younger patients, some adolescents, and a few adults, deep sedation or general anesthesia with endotracheal intubation may be necessary to overcome lack of cooperation, avoid respiratory compromise, and provide adequate time for a complete study.

The facility where TEE occurs should be equipped with oxygen, suction capabilities, drugs, and equipment for cardiopulmonary resuscitation and other emergency therapies. Standard cardiorespiratory monitoring during the procedure includes intermittent blood pressure measurements, electrocardiography, pulse oximetry, and capnography. Patients with CHD may have significant hemodynamic alterations with marginal compensation, requiring the judicious, titrated administration of pharmacologic agents [55]. Patients with cyanotic heart disease are at additional risk for paradoxical air embolism during the administration of intravenous fluids or drugs. Decreases in systemic vascular resistance associated with a sedative or anesthetic agent can worsen right-to-left shunting and exacerbate underlying systemic arterial desaturation, necessitating careful observation of drug responses.

Instrument manipulation and probe controls

Manipulating the TEE probe in several directions aids in imaging cardiovascular structures relative to the sagittal plane (Figure 15.3). The probe shaft can be pushed in (advanced) or pulled back (withdrawn) and can be turned to the right (clockwise) or to the left (counterclockwise). Wheel controls on the probe handle manipulate the probe tip, which can be flexed anteriorly (anteflexed) or posteriorly (retroflexed) and to the right or left (Figure 15.4). Pediatric TEE probes may lack the right-to-left flexion control, seldom a limitation, because only minimal adjustments in the probe's position are needed to navigate from view to view. The imaging plane of a stationary, multiplane transducer can be rotated between angles of 0° and 180°, without the maneuvers required by monoplane and biplane devices to obtain equivalent views [56]. The control to change the multiplane

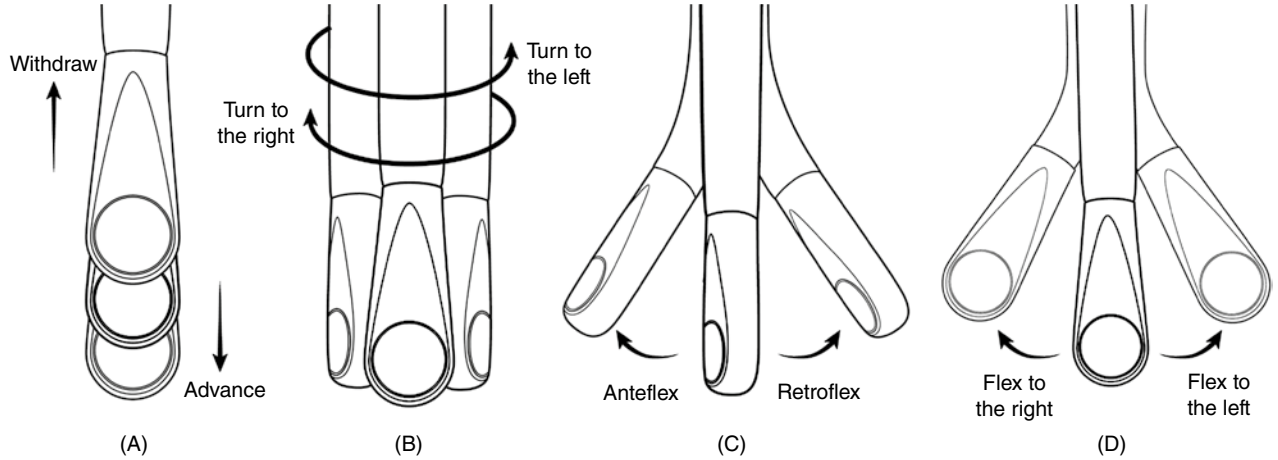


Figure 15.3 *TEE probe manipulation*. The graphic displays the terminology corresponding to the various TEE probe manipulation options. (A) Advance/withdraw; (B) turn to the right/left; (C) anteflex/retroflex; and (D) flex to the right/left. Note that the first two maneuvers (shown in panels A and B) require movement of the entire probe shaft, while performing the second two (depicted in panels C and D) is by special controls that move only the probe tip. (Source: Texas Children's Hospital. Reproduced with permission.)

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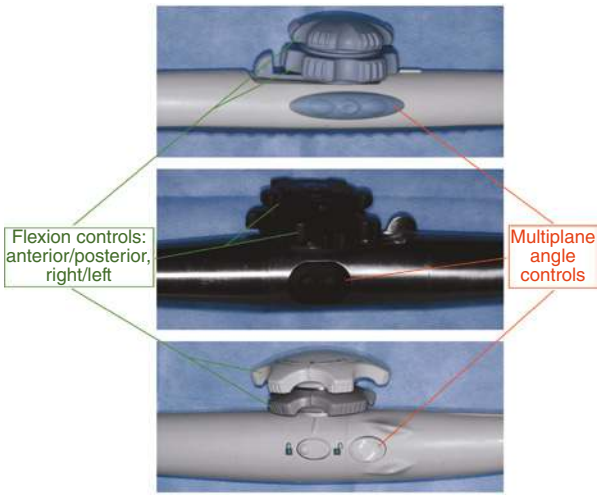


Figure 15.4 *Adult multiplane TEE probe controls.* This photograph shows three different types of commercially available multiplane TEE adult probes with their respective flexion (anterior/posterior, right/left) and multiplane angle controls.

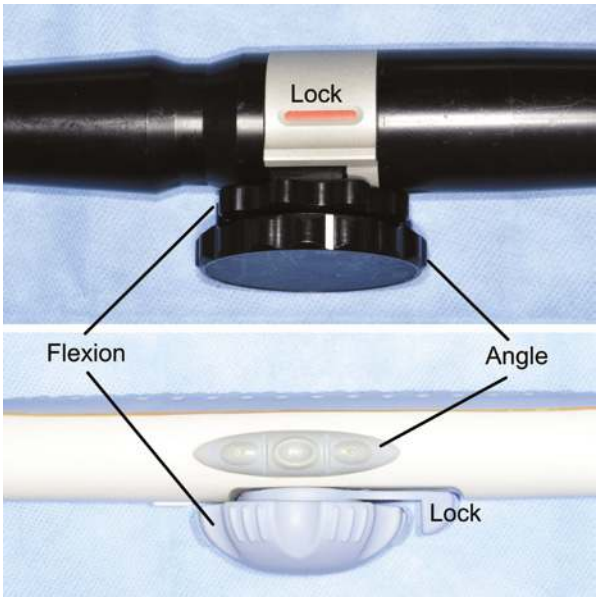


Figure 15.5 *Pediatric multiplane TEE probes.* The photograph displays two commercially available pediatric multiplane TEE probes to highlight differences in the multiplane angle control (mechanical in top panel vs. electronic in lower panel), the wheel control for flexion (anteflexion/retroflexion), and the probe tip locking mechanism.

angle in adult devices is electronic, whereas it can be either mechanical or electronic in pediatric devices (Figure 15.5).

KEY POINTS: TEE HARDWARE

- The TEE technology has evolved from monoplane, to biplane, to multiplane, to recent 3D-live imaging devices.
- Currently, there are four available multiplane probes for TEE imaging in patients with CHD (i.e., neonatal, pediatric, adult 2D, and adult 3D TEE probes).
- All multiplane probes include 2D, M-mode, spectral Doppler, and color Doppler capabilities.
- Two main factors guide device selection: probe size and patient weight.

TEE examination in CHD

Structural examination

The echocardiographic evaluation of the patient with CHD presents many challenges because of factors such as the wide spectrum of lesions; the myriad of anatomic variants, each with specific physiologic alterations; the frequent presence of coexistent pathologies; and the complexity of many defects [1]. Compounding these considerations is the need to be able to reconstruct the 3D anatomy of the congenitally malformed heart while relying primarily, and in most instances exclusively, on 2D imaging. Despite these challenges, TEE permits excellent visualization of cardiovascular structures and provides significant benefits.

A comprehensive TEE examination in the patient with CHD can employ different approaches. Each approach has specific advantages and some potential disadvantages, as described briefly in the sections that follow.

View-based approach

The "view-based" TEE examination relies on obtaining several specific predefined cross sections by moving the probe to various locations within the esophagus or stomach. Initial guidelines by the ASE and Society of Cardiovascular Anesthesiologists (SCA) suggested a set of 20 TEE views for a comprehensive examination. This widely adopted approach became standard practice for the TEE examination of the adult patient with an anatomically normal heart [57]. Subsequently, updated recommendations incorporated 8 additional cross sections, for a total of 28 TEE views (Figure 15.6) [3]. Recent ASE TEE guidelines specifically addressing children and all patients with CHD recommend 28 views for a comprehensive examination [5]. Most of these views are the same described for imaging of the adult heart, but a few were added in recognition of the need for examination of specific structures or pathologies commonly seen in the pediatric age group or the congenital population (Figure 15.7). Selected adult TEE views were correspondingly excluded to maintain the same overall number of cross sections. A more detailed description of views useful in imaging CHD appears in the subsequent sections. During a complete TEE examination, obtaining most or all these views, regardless of sequence, provides comprehensive anatomic, functional, and hemodynamic information. This approach helps the practitioner learn the basic principles of TEE and represents an excellent foundation on the subject. The reader is referred to the outstanding web-based educational resources of the Toronto General

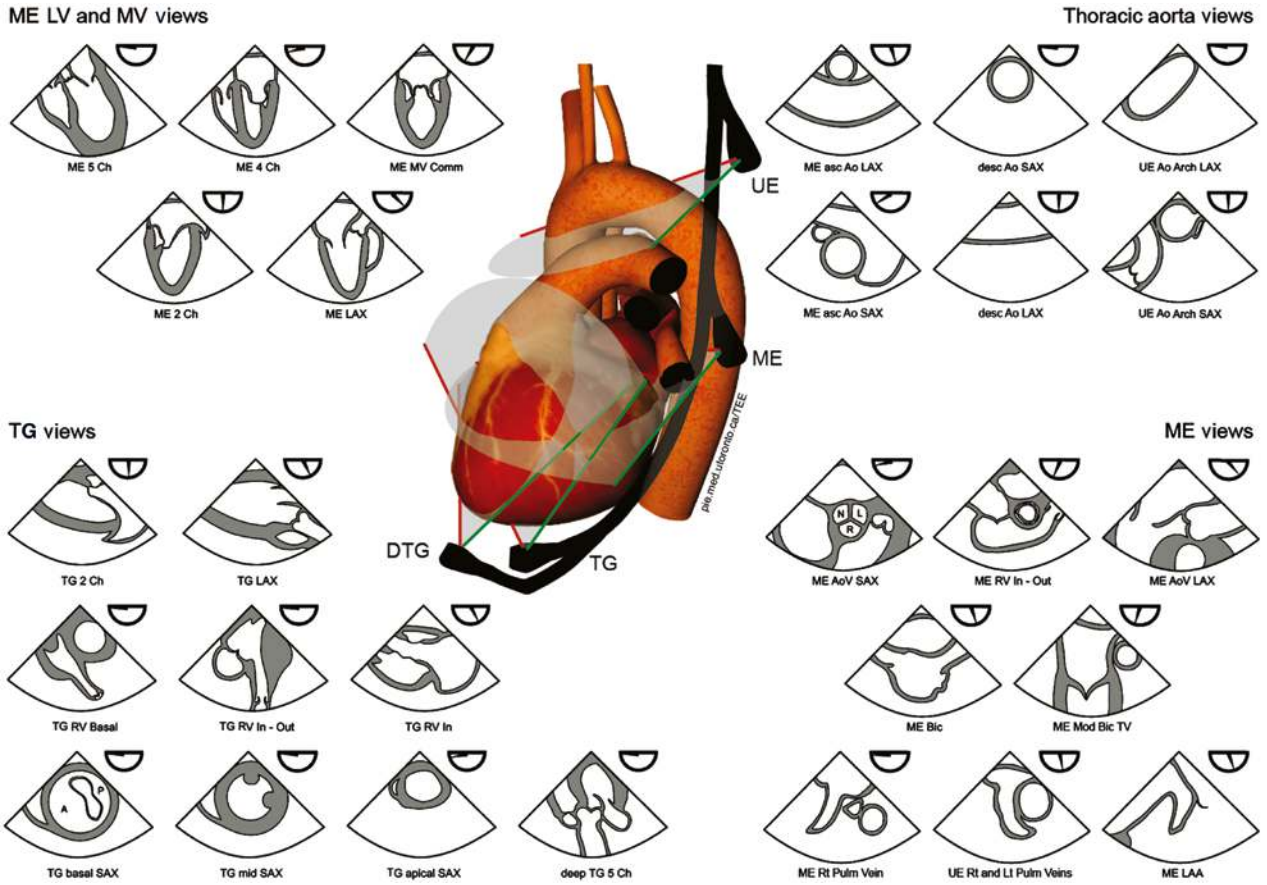


Figure 15.6 *TEE views in the comprehensive adult examination*. This graphic displays the suggested 28 views in the adult guidelines for a comprehensive TEE examination [3]. The TEE probe positioned at the upper esophageal (UE), midesophageal (ME), transgastric (TG), and deep transgastric (DTG) levels can attain these cross sections. The grouping of the views in this graphic is by the structures being interrogated or the specific TEE window. The reader is referred to this publication for a detailed description of each of these views. *A* anterior; *L* left coronary cusp; *LV* left ventricle; *MV* mitral valve; *N* con coronary cusp; *P* posterior; *R* right coronary cusp. (Source: Ms. Willa Bradshaw. Reproduced with permission.)

Hospital (www.pie.med.utoronto.ca/TEE/) for interactive modules on the standard adult TEE examination.

The view-based TEE examination has substantial benefits, not only as a standardized method of performing the evaluation but also in terms of facilitating teaching, archiving, and reporting of the study, as well as quality assurance. Familiarity with these views, including the nomenclature, where and how to obtain each, the structures displayed by each, and the information derived, enhances one's ability to perform a detailed examination and to communicate the findings to others.

However, this approach has several limitations. The most recent pediatric and congenital TEE guidelines highlight two of them. First, the suggested TEE views were aimed primarily at the intraoperative interrogation and excluded views that may be necessary in nonoperative settings. Second, the outlined TEE examination was not diagnosis based, potentially excluding important views in the evaluation of specific cardiac conditions. These limitations are particularly relevant to the assessment of CHD, because a strict view-based approach is inadequate for the detailed evaluation of structural abnormalities in many patients. Standard TEE views may not allow imaging of the complex anatomic relationships that characterize congenital pathology. Of critical relevance is that comprehensively evaluating many structural anomalies requires not only single views but also sweeps between multiple planes, some modified or nonstandard, aimed at building a 3D construct of the anatomic abnormalities.

Structure-based approach

The "structure-based" examination focuses on detailed TEE imaging of cardiovascular structures of interest by using complementary views to permit their in-depth examination. Specific structural imaging in the adult has been described, for example, in the detailed evaluation of cardiac valves, the Ao, and the LAA, among other regions [3, 58–64]. A similar type of approach has been extremely helpful in characterizing specific anatomic and functional abnormalities in the patient with CHD, such as defects that involve the atrial or ventricular septum, pulmonary veins, and other structures [65–67].

This type of image-acquisition paradigm may be preferable when, for various reasons, a focused TEE examination needs to address only a specific pathology of concern. One potential limitation of this approach in CHD is that by targeting only particular cardiac structures or pathologies, one may overlook relevant coexisting

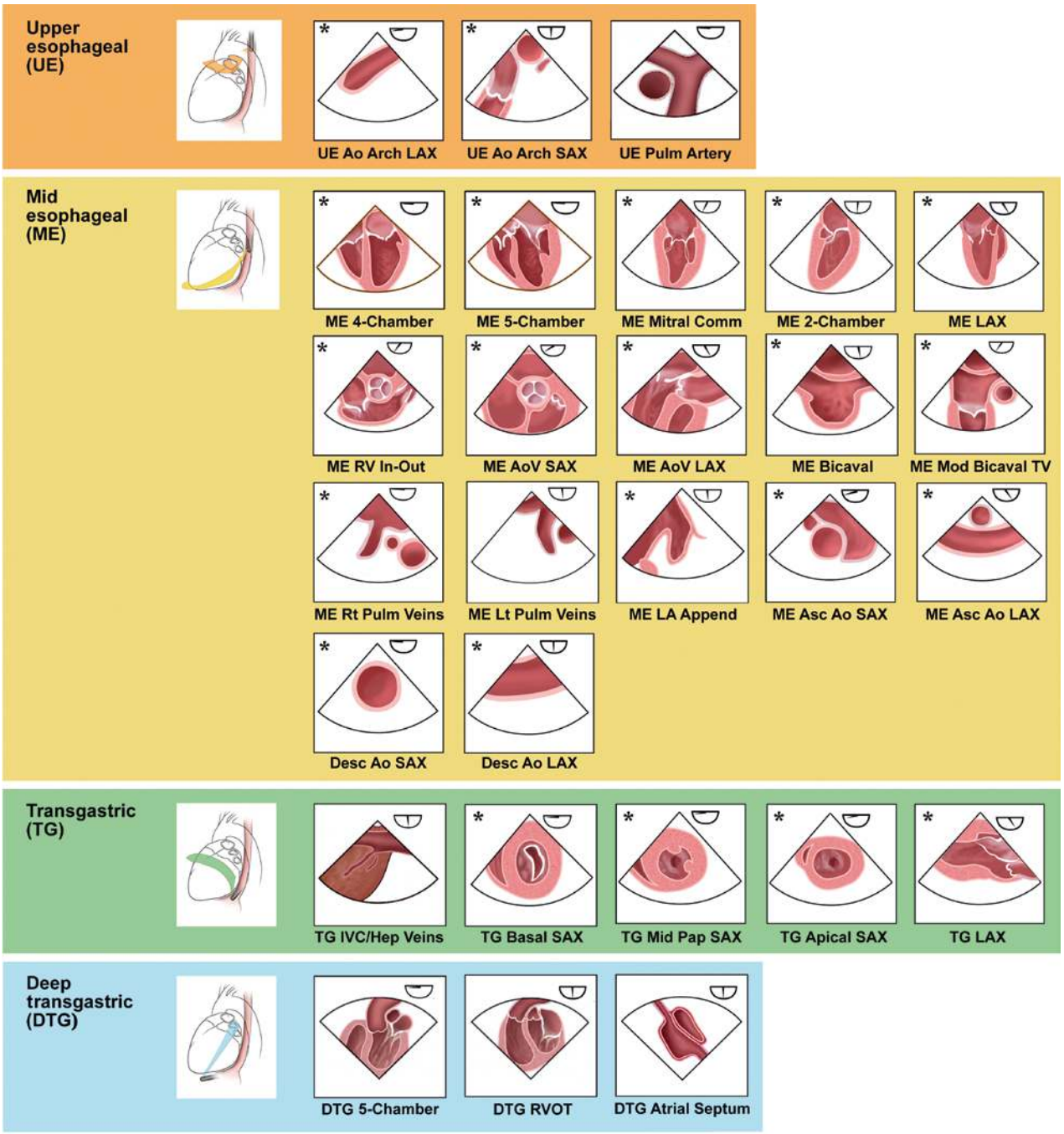


Figure 15.7 *TEE views in the comprehensive pediatric and congenital TEE examination*. The graphic displays the 28 recommended TEE views as a starting point in the guidelines addressing the comprehensive examination in children and all patients with CHD [5]. The grouping of the views in this figure is by the specific TEE window that the views can be obtained. The reader is referred to this publication for a detailed description of each of these views. (Sources: Texas Children's Hospital. Reproduced with permission; panels marked by asterisk from Hahn et al. [3]. Reproduced with permission of Elsevier.)

abnormalities or anatomic variants. However, by examining all relevant structures, this is the favored examination approach in CHD [5].

Sequential segmental approach

The "sequential segmental" analysis has been proposed as the foundation of complete anatomic assessment in CHD [68–71]. This approach involves a well-organized, methodical interrogation of the three major cardiac segments (i.e., atria, ventricles, and great arteries) and their relationships to each other (connections or alignments between the segments), to define a patient's anatomy and any abnormalities (Figure 15.8; also refer to Chapter 7). The incorporation of this type of analysis into many diagnostic imaging modalities in CHD is key in echocardiographic assessment (TTE and fetal imaging) [72–75].

The fundamental principle of this methodology is the identification of specific cardiac chambers by their characteristic

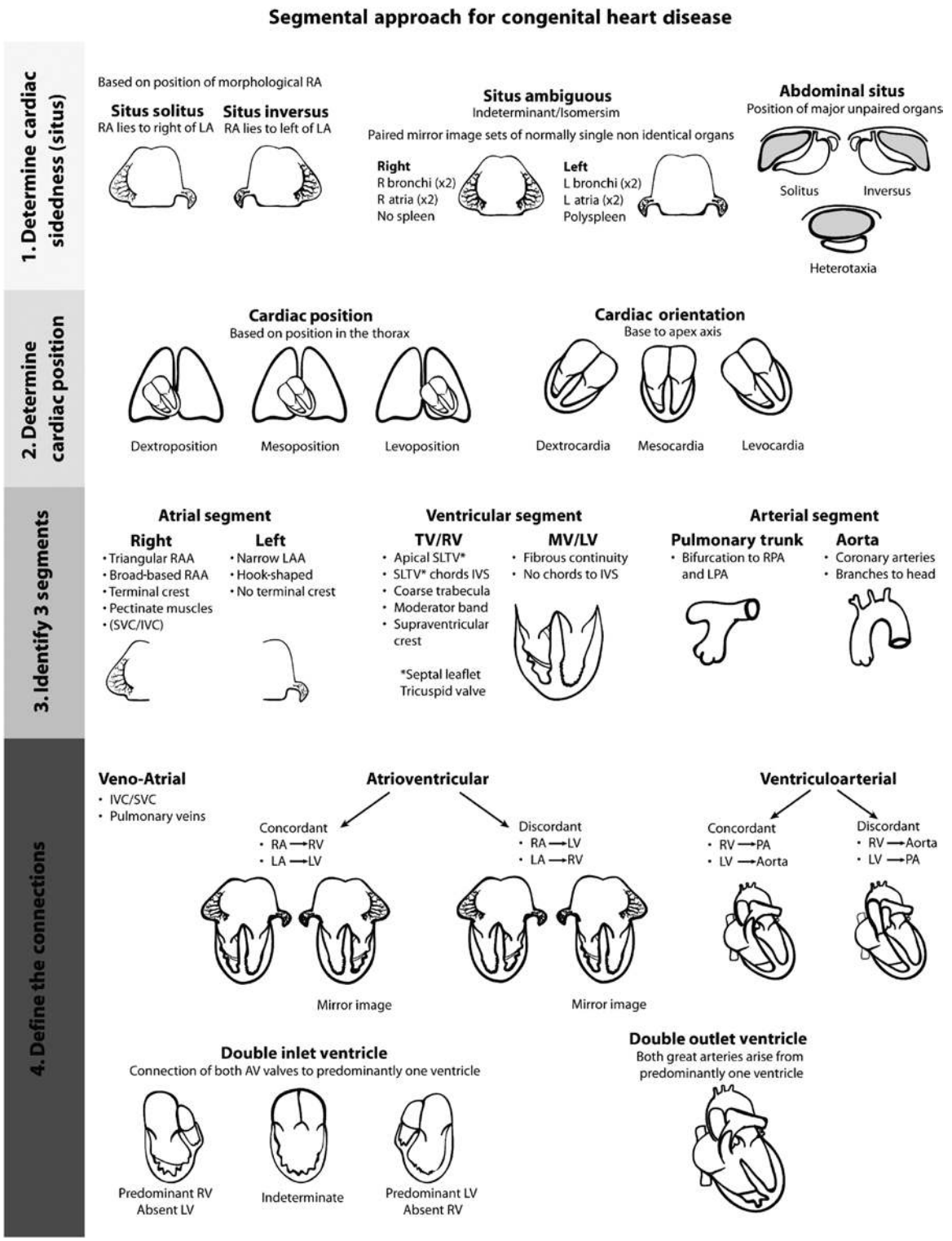


Figure 15.8 *Sequential segmental analysis*. The graphic illustrates the steps involved in the diagnostic analysis of CHD. The approach examines the following: cardiac situs; position of heart in the thorax and base to apex orientation; all segments and connections; and the cardiac defects. *AV* atrioventricular; *IVC* inferior vena cava; *IVS* interventricular septum; *L* left; *LA* left atrium; *LAA* left atrial appendage; *LPA* left pulmonary artery; *LV* left ventricle; *MV* mitral valve; *PA* pulmonary artery; *R* right; *RA* right atrium; *RAA* right atrial appendage; *RPA* right pulmonary artery; *RV* right ventricle; *SVC* superior vena cava; *TV* tricuspid valve. (Source: Figure courtesy of Ms. Willa Bradshaw.)

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morphologic properties, rather than by their positions within the body. The suggested practice examines the arrangement of the thoracoabdominal organs or situs, atrial structures, ventricles, and great arteries, as well as the connections between the segments, namely, the atrioventricular (AV) and ventriculoarterial (VA) connections [76, 77]. This approach has significant merit as congenital heart lesions can have normal or abnormal relationships among chambers, valves, and vessels (refer to Chapter 7).

The sequential segmental analysis overcomes the limitations of a purely structure-based approach, as careful interrogation and identification of all cardiovascular structures ensures a thorough TEE assessment. Despite these advantages, for those unfamiliar with segmental anatomy, the methodology involved may be less intuitive and more time-consuming. However, this approach is very useful, particularly in a preoperative study performed to characterize or confirm the anatomic abnormalities.

The TEE examination

Guidelines and recommendations exist for the application of TTE and TEE imaging in CHD [1, 3, 5–8]. Previous publications have addressed applications of TEE in CHD [10, 78], with the most recent guidelines outlining in detail the comprehensive and systematic examination in these patients [5]. Providing details of the TEE examination in CHD is beyond the scope of this chapter, so we review only selected aspects, and the reader should look to other publications for an exhaustive discussion on the subject [5, 28, 79, 80].

Although there is no predetermined sequence for the order of acquisition of information during a TEE examination in CHD, and one should not be inferred from the following outline, it is valuable for individuals to develop their own organized approach to performing a complete and expeditious interrogation. Unique patient conditions or specific circumstances, such as hemodynamic instability or respiratory impairment by TEE probe manipulation, may shorten the examination.

The sections that follow on imaging windows and planes provide a brief overview of selected TEE views frequently obtained during CHD evaluation. The examination assumes levocardia (heart in the left thoracic cavity with apex pointing to the left) and normal segmental anatomy: in other words, visceroatrial situs solitus (stomach on the left, liver on the right, and normal atrial arrangement), concordant AV and VA connections, normal ventricular topology, and great artery spatial orientation. It may not be possible to obtain all views in all patients, nor will the planes and angles of interrogation necessarily conform to each patient's unique anatomy. The variety of structural cardiovascular malformations dictates a modified scheme in many cases.

The comprehensive TEE examination in CHD includes detailed 2D imaging and meticulous spectral and color-flow Doppler interrogation. Contrast echocardiography using an injection of agitated saline or 5% albumin into a peripheral or central vein can detect small intracardiac shunts, further delineate anatomy (e.g., persistent left superior vena cava [SVC]–to–coronary sinus connection), and identify pathology such as atrial baffle leaks [81, 82].

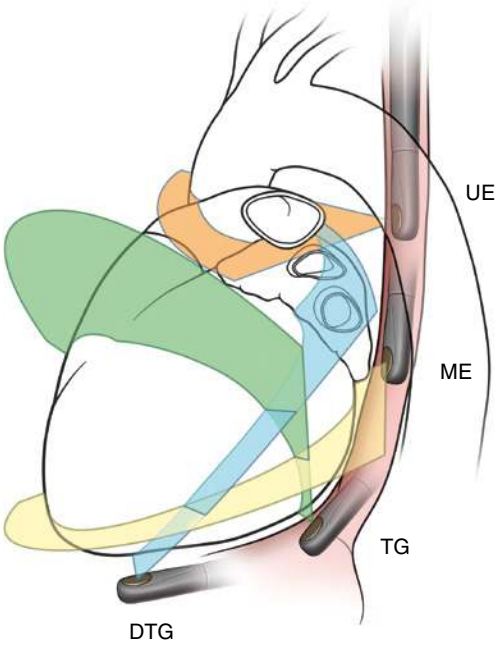


Figure 15.9 *TEE imaging windows*. The standard TEE imaging windows and representative imaging planes are shown. *DTG* deep transgastric; *ME* midesophageal; *TG* transgastric; *UE* upper esophageal positions. (Source: Texas Children's Hospital. Reproduced with permission.)

Imaging windows

During a TEE examination in CHD, imaging of the heart and related vascular structures occurs at multiple levels: upper esophageal (UE), midesophageal (ME), TG, and DTG (Figure 15.9). Different transducer angles are used to obtain specific cross sections. These diverse TEE windows complement each other and provide information that is not otherwise obtainable in some views. The TG and DTG views, for example, provide favorable alignment of the Doppler angle of interrogation to the outflow tracts, optimizing spectral Doppler signals and the assessment of gradients.

Multiplane imaging views

The guidelines for performing a comprehensive TEE examination in children and all patients with CHD describe in detail the recommended 28 tomographic views, acquisition protocol, and structures imaged in each of these cross sections (Figure 15.7). The reader is referred to this document for further information [5]. Table 15.5 highlights how these multiplane TEE views can be obtained (note that this is a succinct guide, as there are several approaches), structures displayed, and relevant features of each. As emphasized in the guidelines document, these views are only a starting point, as additional, modified, nonstandard cross sections may be necessary to define the anatomy of a given patient. This is particularly important in patients with complex anatomy, such as seen in heterotaxy, and in patients with cardiac malpositions, for whom the multiplane transducer angles for the standard views may need to be significantly altered.

Table 15.5 Transesophageal echocardiography (TEE) views for a comprehensive examination in children and all patients with congenital heart disease

View (*abbreviation*)	Acquisition details	Structures imaged and assessment
Midesophageal views		
ME Four-chamber view (*ME 4-Ch*)	Neutral probe position, transducer angle of ~0°–10° Equivalent to TTE apical 4-Ch view	All four cardiac chambers, AV valves, atrial and ventricular septa, CS
ME Five-chamber view (*ME 5-Ch*)	From ME 4-Ch view probe tip anteflexion or probe withdrawal	In addition to structures in the ME 4-Ch view, LVOT, proximal Ao
ME Mitral valve view (*ME Mitral*)	From ME 4-Ch view increase transducer angle to ~50°–70°	LA, LV, MV (segments, commissures), tensor apparatus, papillary muscles, CS
ME Two-chamber view (*ME 2-Ch*)	From ME 4-Ch view increase transducer angle ~80°–100° Orthogonal to the ME 4-Ch view	LA, LAA, MV, LV, CS
ME Long-axis (*ME LAX*)	From ME 4-Ch view increase transducer angle to ~120°–140°	LA, LV, RVOT, LVOT, MV, AoV, prox Asc Ao aorta
ME Aortic valve long-axis (*ME AoV LAX*)	From ME LAX view reduce image depth	Focused view of LVOT, AoV, prox Asc Ao
ME Aortic valve short-axis (*ME AoV SAX*)	From ME 5-Ch view keep Ao root in focus, withdraw probe, adjust transducer plane to 25°–45° Orthogonal to ME AoV LAX view	AoV morphology (number of cusps, commissures), function, localization of pathology (stenosis, regurgitation)
ME Ascending aorta long-axis (*ME Asc Ao LAX*)	From ME LAX view withdraw probe, adjust transducer angle to ~90°–110°	Asc Ao in long axis, RPA Allows for assessment of proximal to mid ascending aortic pathology
ME Ascending aorta short-axis (*ME Asc Ao SAX*)	From ME Asc Ao LAX view decrease transducer angle to ~0°–30° Orthogonal to ME Asc Ao LAX view	Prox Asc Ao (short axis), MPA (long axis), RPA, SVC Allows for Doppler assessment of MPA
ME Right ventricular inflow-outflow (*ME RV In-Out*)	From ME 4-Ch, ME 5-Ch, or ME AoV SAX anteflex probe tip, rotate transducer angle to ~50°–70° Mimics inverted TTE parasternal SAX view at base of heart	RA, LA, IAS, TV, PV, AoV, MPA, inflow and outflow of RV Useful to assess VSDs, TR jets, RV size, function, and obstruction
ME Bicaval view (*ME Bicaval*)	Transducer angle of 90°–110° Orthogonal to ME 4-Ch view	SVC and IVC entry to RA, RAA, IAS; useful to assess IAS, central catheter tip position
ME Modified Bicaval tricuspid valve (*ME Mod Bicaval TV*)	Transducer angle of 50°–70° or from ME Bicaval view turn probe to the right	TV (anatomy, regurgitation severity, regurgitant Doppler peak velocity), LA, RA
ME Left atrial appendage view (*ME LAA*)	Transducer angle of ~90°–110° LAA also seen in ME 4-Ch view with LA centered and probe shaft turned to left	LAA, variable anatomy of LAA requires multiple views for a detailed examination
ME Right pulmonary veins (*ME Rt Pulm veins*)	From ME 4-Ch view, turn probe shaft to right at transducer angle 0°, adjusting to 30°–50° may display all right-sided pulmonary veins Alternate approach is to turn the probe to the right from the ME Bicaval view	Right pulmonary veins, SVC, Mid Asc Ao
ME Left pulmonary veins (*ME Lf Pulm veins*)	After centering LA in screen rotate transducer angle to 90°–110° and turn probe shaft to the left Alternate approach is from the ME 4-Ch view to turn probe to the left to image the LAA, and slowly advance–withdraw the probe	Left pulmonary veins, LPA
Transgastric views		
TG Basal short-axis (*TG Basal SAX*) TG Mid-papillary short-axis (*TG Mid Pap SAX*) TG Apical short-axis (*TG Apical SAX*)	Gently advance TEE probe into the lower esophagus/stomach, with slight anteflexion at transducer angle of ~0°–20°	Multiple cross-sectional short-axis views of LV at basal, mid-papillary, and apical levels TG Mid Pap SAX view extremely helpful in evaluating LV function (global and segmental), LV preload
TG Long-axis (*TG LAX*)	From TG Mid Pap view increase transducer angle to ~120°–140°	LV (long axis), LVOT, AoV Useful for Doppler evaluation of Ao outflow

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Table 15.5 (Continued)

View (*abbreviation*)	Acquisition details	Structures imaged and assessment
TG Inferior vena cava/Hepatic veins (*TG IVC/Hep veins*)	From ME Bicaval view advance probe into the distal esophagus or upper gastric region at transducer angle of ~80°–100°	IVC, hepatic veins, RA Useful to assess situs and evaluate flow in venoatrial connection (IVC–RA), hepatic veins, anomalous pulmonary veins
Deep transgastric views		
DTG Five-chamber view (*DTG 5-Ch*)	Advance probe further into stomach with transducer angle of 0°–20° and variable degrees of tip anteflexion LV is displayed from base at top to apex at bottom of image (in contrast to standard adult TEE view) Nearly equivalent to ME 5-Ch view	Ventricles, LVOT, Ao root, IVS, MV
DTG Right ventricular outflow tract (*TG RVOT*) Not a standard view in the adult TEE guidelines	From DTG 5-Ch view rotate transducer angle to ~50°–90° At times, rightward probe shaft rotation can be helpful	Ventricles, RVOT, MPA, IVS, MV
DTG Atrial septal (*TG Atr Sept*) Not a standard view in the adult TEE guidelines	From the DTG RVOT view turn probe shaft right with a transducer angle to ~80°–90° Simulates TTE subcostal bicaval view	Excellent delineation of IAS and systemic venous connections Visualizing the IVC may require a transducer angle of ~100°–120°)
Upper esophageal views		
UE Pulmonary artery view (*UE PA*) Not a standard view in the adult TEE guidelines	From ME 4-Ch view withdraw TEE probe, anteflex tip, turn shaft left at a transducer angle of ~0°–20° Alternatively, from ME RV In-Out view withdraw probe and adjust transducer angle	MPA and branches Useful to assess main PA, bifurcation, proximal branches, and to perform Doppler exam Interposition of left mainstem bronchus, makes imaging LPA difficult
UE Aortic arch long-axis (*UE Ao Arch LAX*)	Position probe in upper esophagus with transducer angle of ~0°–10°	Aortic arch (long axis), innominate vein
UE Aortic arch short-axis (*UE Ao Arch SAX*)	From UE Ao Arch LAX increase transducer angle to ~70°–90° Orthogonal to UE Ao Arch LAX	Aortic arch (short axis), innominate vein, PV, MPA and branch PAs (with probe shaft rotation)
Aorta views		
Descending aorta in short-axis (*Desc Ao SAX*)	From ME 4-Ch view rotate probe shaft left to display the left-sided pulmonary veins and LAA, turning probe further posteriorly shows the Desc Ao SAX at a transducer angle ~0°–10°	Desc Ao (short axis)
Descending aorta in long-axis (*Desc Ao LAX*)	From desc Ao SAX view increase transducer angle to ~90°–100° (orthogonal to Desc Ao SAX view)	Desc Ao (long axis)

Abbreviations: *Ao* aorta; *AV* atrioventricular; *Asc* ascending; *CS* coronary sinus; *Desc* descending; *IAS* interatrial septum; *IVC* inferior vena cava; *IVS* interventricular septum; *LA* left atrium; *LAA* left atrial appendage; *LPA* left pulmonary artery; *LV* left ventricle; *LVOT* left ventricular outflow tract; *MPA* main pulmonary artery; *MV* mitral valve; *PA* pulmonary artery; *PV* pulmonary valve; *Prox* proximal; *RA* right atrium; *RAA* right atrial appendage; *RPA* right pulmonary artery; *RV* right ventricle; *RVOT* right ventricular outflow tract; *SVC* superior vena cava; *TR* tricuspid regurgitation; *TTE* transthoracic echocardiography; *TV* tricuspid valve; *VSD* ventricular septal defect

In general, the views can be considered as follows:

ME views

A significant amount of TEE imaging takes place in the ME region; in fact, this window allows acquisition of more than half of the suggested views (15/28) for a comprehensive pediatric or adult CHD examination. The *ME four-chamber view (ME 4-Ch)* is considered the starting view or "home base," as it acts as a reference point for obtaining other views by manipulating the probe (tip or shaft adjustments) or adjusting the transducer angle on a multiplane probe.

TG views

The TG views include five cross sections of the heart. Transverse plane imaging shows the ventricles in short axis at various levels from base to apex. Longitudinal plane imaging shows the left ventricle (LV) and right ventricle (RV) and the inferior cavoatrial region.

DTG views

Advancing the probe into the fundus of the stomach obtains the three DTG views. Up-down inversion displays the TEE images in an anatomic orientation (base of the heart at the

top of the sector and apex at the bottom), which assists tremendously in the understanding of complex disease and correlates to TTE imaging and other diagnostic modalities. This convention is not applied to standard adult TEE DTG imaging, or to equivalent apical or subcostal views obtained by surface imaging in the adult patient. The DTG views of the semilunar valves or ventricular outflow tracts provide excellent angles of spectral Doppler interrogation, thereby allowing optimal alignment of the cursor parallel to the direction of blood flow. These views also significantly contribute to the evaluation of VA connections in CHD.

UE views

These three views allow imaging of vascular structures (e.g., pulmonary artery [PA], aortic arch, variants or anomalies).

Aortic views

The views of the thoracic descending Ao can be obtained at various levels by withdrawing and advancing the imaging probe. The level of the Ao in these views can be difficult to interpret because of the lack of landmarks.

Three-dimensional TEE

Ease of acquisition with rapid online display of detailed dynamic images has increased the use of real-time 3D TEE in the perioperative period to assess cardiac anatomy and function [4, 40, 41, 83–85]. Special matrix array ultrasonography probes acquire raw data by volume scanning, and integrated ultrasonography machine software processes the 3D data sets. These TEE probes perform all standard 2D functions, include motion mode (M-mode) and all Doppler modalities (e.g., spectral, color, tissue), and have the additional feature of multiplane mode (X-plane) to simultaneously display independent 2D scanning planes during the same heartbeat. Single-button activation of specific 3D imaging modes for both TEE and TTE matrix array probes include live, zoom, full volume, and color Doppler full volume, allowing for real-time imaging of cardiac structures (Table 15.6). Using these modes, one can define a specific region of interest to obtain a 3D volume of varying sizes. Newer software can display all 3D data sets in real time, such that moving the probe will immediately affect the 3D volume on the display.

Currently, all real-time 3D imaging modes appear as a volume-rendered 3D object with full details of the surface and inner structure. The free rotation of any rendered 3D object on the screen allows its display from any orientation, including the surgeon's perspective.

Cropping permits a "virtual dissection" of the 3D object that examines all its details. The 3D technology has proven superior to 2D echocardiography for assessing the LV (volume, ejection fraction [EF], mass, and dyssynchrony) and the mitral valve (MV) [86]. *En face* views of the MV, for example, when displayed in the surgeon's orientation viewed from the left atrium (LA), show the anatomical details of the leaflets and define leaflet pathology of prolapse, clefts, and perforations [87, 88]. Thus, the use of this modality has become well accepted for adult patients undergoing cardiothoracic surgical interventions and catheter-based procedures. The excellent detail of 3D imaging provides more information about cardiac anatomy and spatial relationships than 2D echocardiography, clearly a merit of the technology in evaluating CHD. Real-time 3D TEE can better show the intricate relations of cardiac structures in patients with complex CHD. While multiple 2D views were previously necessary to assess pathology, 3D imaging can show the entire heart in a single screen display. In assessing CHD, 3D TEE has a major role in evaluating defects in both the atrial and ventricular septum and valvular pathologies of the MV and aortic valve (AoV) [4, 89]. Current recommendations for 3D TEE imaging in CHD appear in Table 15.7 [5].

Although experience with real-time 3D TEE in children with CHD is limited by the lack of suitable imaging devices, applications of the technology have shown extremely favorable results [4, 21, 65, 66, 89–95], mirroring the reported 3D TTE experience in CHD [96, 97]. It is reasonable to consider this modality in cases for which a 3D perspective may offer additional benefits over routine 2D TEE in the patient suitable for 3D TEE imaging with currently available devices.

Similar to 2D TEE, structures closest to the probe are easily imaged in 3D, enabling the evaluation of clinically relevant issues in real time. The thin interatrial septal (IAS) and distant structures (AoV and pulmonary valve [PV]) remain difficult to image by 3D TEE in some patients. Despite recommendations

Table 15.6 Real-time three-dimensional transesophageal echocardiography imaging

Structure	2D view for 3D acquisition	3D mode	Clinical utility
Mitral valve	ME 4-Ch (0°), ME MV Comm (60°), ME 2-Ch (90°), ME LAX (120°); ± CD for all views	Zoom, FV	Morphology, function, quantification (effective regurgitant orifice area, MV area)
Aortic valve	ME AoV SAX (30°–60°), ME AoV LAX (120°); ± CD for all views	Zoom	AoV area, TAVI
Tricuspid valve	ME 4-Ch (0°–30°), TG (40°); ± CD for all views	Zoom	Unstudied
Pulmonary valve	UE Ao Arch SAX (90°) ± CD	Zoom	TEE has limited views
Interatrial septum	ME 4-Ch (0°), ME Bic (90°); ± CD for all views	Zoom, FV	ASD
Left ventricle	ME 4-Ch (0°), ME 2-Ch (90°), ME LAX (120°)	FV	Volume, mass, ejection fraction, dyssynchrony
Right ventricle	ME 4-Ch (0°), ME 2-Ch (90°), ME LAX (120°)	FV	Volume, ejection fraction
Left atrial appendage	ME 4-Ch (0°), ME MV Comm (60°), ME 2-Ch (90°), ME LAA (110°)	Live, Zoom	Thrombus

The standard 2D transesophageal echocardiography (TEE) view is used with different 3D imaging modes to scan a region of interest and obtain a volume of tissue. This volume or block of tissue can be cropped, rotated, and displayed in any orientation to show normal and pathologic findings.
Abbreviations: 2D two-dimensional; *3D* three-dimensional; *AoV* aortic valve; *ASD* atrial septal defect; *Bic* bicaval; *CD* color Doppler; *Comm* commissural; *FV* full volume; *LAA* left atrial appendage; *LAX* long-axis; *ME* midesophageal; *MV* mitral valve; *SAX* short-axis; *TAVI* transcatheter AoV implantation; *TG* transgastric; *UE Ao Arch* upper esophageal aortic arch; *2-Ch* two-chamber; *4-Ch* four-chamber

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Table 15.7 Clinical use of three-dimensional (3D) transesophageal echocardiography (TEE) in congenital heart disease

3D TEE has been recommended for
- ASD device closure guidance
- VSD device closure guidance
- Visualization of catheters, delivery systems, and devices
- Measurement of defects visualized in *en face* views
- Analysis of the anatomy and function of atrioventricular valves
- Visualization of the aortic valve and left ventricular outflow tract

3D TEE has been used effectively during
- Fontan fenestration closure
- Ruptured sinus of Valsalva aneurysm device closure
- Coronary artery fistula device closure
- Prosthetic valve paravalvular leak device closure
- Atrial switch baffle leak device closure and baffle obstruction stenting
- Atrial septum transseptal puncture during various procedures
- Biventricular pacemaker synchrony assessment and lead placement guidance

Abbreviations: *ASD* atrial septal defect; *VSD* ventricular septal defect-
Source: Reproduced from Puchalski et al. [5], with permission Elsevier.

for 3D echocardiographic image acquisition and display, a consensus statement on 3D imaging in CHD, and the reported clinical use of 3D TEE in the pediatric and CHD TEE guidelines, there remains no standardized protocol for the use of intraoperative real-time 3D TEE in everyday practice [4, 5, 83]. Although 3D image acquisition is rapid, processing the 3D data sets with analytical software can be time-consuming and challenging in the hectic intraoperative environment.

Functional assessment

Assessment of ventricular function is an important component of a comprehensive TEE examination. While it is common to evaluate systolic function, evaluating diastolic function is an area of growing interest because there is increasing recognition of the role that diastolic dysfunction plays in clinical outcomes [98].

The ventricles differ in geometry, systolic contraction pattern, and load conditions, requiring different methods to assess each chamber. Quantitative assessment of LV systolic function by echocardiography relies on geometric models that may not be applicable to the unusual ventricular geometries typical of CHD [2, 99]. In patients with CHD, the extents of RV enlargement and deterioration of function often determine the need for clinical intervention [100]. Currently, CMR is the gold standard for assessing RV systolic function [101], whereas real-time 3D echocardiography is comparable to CMR in assessing LV function [83].

Newer echocardiographic techniques can quantify subtle changes in regional and global ventricular function, independent of ventricular morphology, and are less affected by loading conditions [102]. *Tissue Doppler imaging* (TDI), also referred to as *Doppler tissue imaging*, provides a reproducible, clinically valid, and easily obtainable nongeometric quantitative method to assess both systolic and diastolic ventricular function [103]. *Strain* and *strain rate imaging* can provide global and regional assessment of ventricular function that is independent of geometry and less affected by loading conditions [104–106]. Improved ultrasonography technology has simplified techniques such as TDI, 3D EF, and tissue tracking for strain and strain rate to better quantify systolic function in the operative setting [107, 108]. For many of these techniques, there are reference values for normal adults and children, most often established by TTE [2, 99, 109, 110]. These values vary greatly according to age and lack validation by TEE. The discussion that follows highlights general concepts regarding selected approaches for assessing ventricular function by echocardiography.

LV systolic function

Normal LV function involves complex 3D movements during the cardiac cycle. Systolic function depends on heart rate, myocardial contractility, and loading conditions. Typically, quantitative echocardiographic assessment of LV function measures changes in LV volume by calculating stroke volume (SV), LV ejection fraction (LVEF), and cardiac output (CO). However, these quantitative measures are time-consuming, limited by loading conditions, and affected by alterations in geometric shape. Technical concerns when using TEE, such as chamber foreshortening and poor endocardial definition, further complicate the acquisition of quantitative information. Thus, intraoperative ventricular systolic performance is often assessed qualitatively, most commonly by "eyeballing" and at times by using methods such as simple linear (shortening fraction [SF]) and area (fractional area change [FAC]) measurements.

"Eyeballing" of wall motion and thickening in the ME 4-Ch, TG Mid Pap SAX, and TG LAX views (refer to Figure 15.7 and Table 15.5) can be used to qualitatively assess ventricular systolic function. Although used ubiquitously, this subjective technique lacks standardization, depends on experience, and has significant inter- and intra-observer variability. The TG Mid Pap SAX view is often used but examines only a portion of the LV (six segments) and may not reflect global systolic function in hearts with an abnormal geometric shape or regional wall motion abnormalities.

SF estimates LV systolic function from linear measures of end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) by using M-mode in a TG Mid Pap SAX view of the LV (Figure 15.10A). The superior temporal resolution of M-mode echocardiography can capture the movement of structures over time. The SF as a percentage (normal: 26–45%) is determined by the following formula:

$$\mathrm{SF}(\%) = \frac{(\mathrm{LVEDD} - \mathrm{LVESD}) \times 100}{\mathrm{LVEDD}}$$

FAC estimates global LV systolic function by using area measurements; thus, it differs from the LVEF, as it is not a volume measurement. Tracing the LV endocardial border obtains an area at end-diastole (LVEDA) and end-systole (LVESA) from LAX (ME view) or SAX (TG view) LV cross sections (Figure 15.10B). The LVFAC expressed as a percentage (normal: 45%) is determined by the following formula:

$$\mathrm{LVFAC}(\%) = \frac{(\mathrm{LVEDA} - \mathrm{LVESA}) \times 100}{\mathrm{LVEDA}}$$

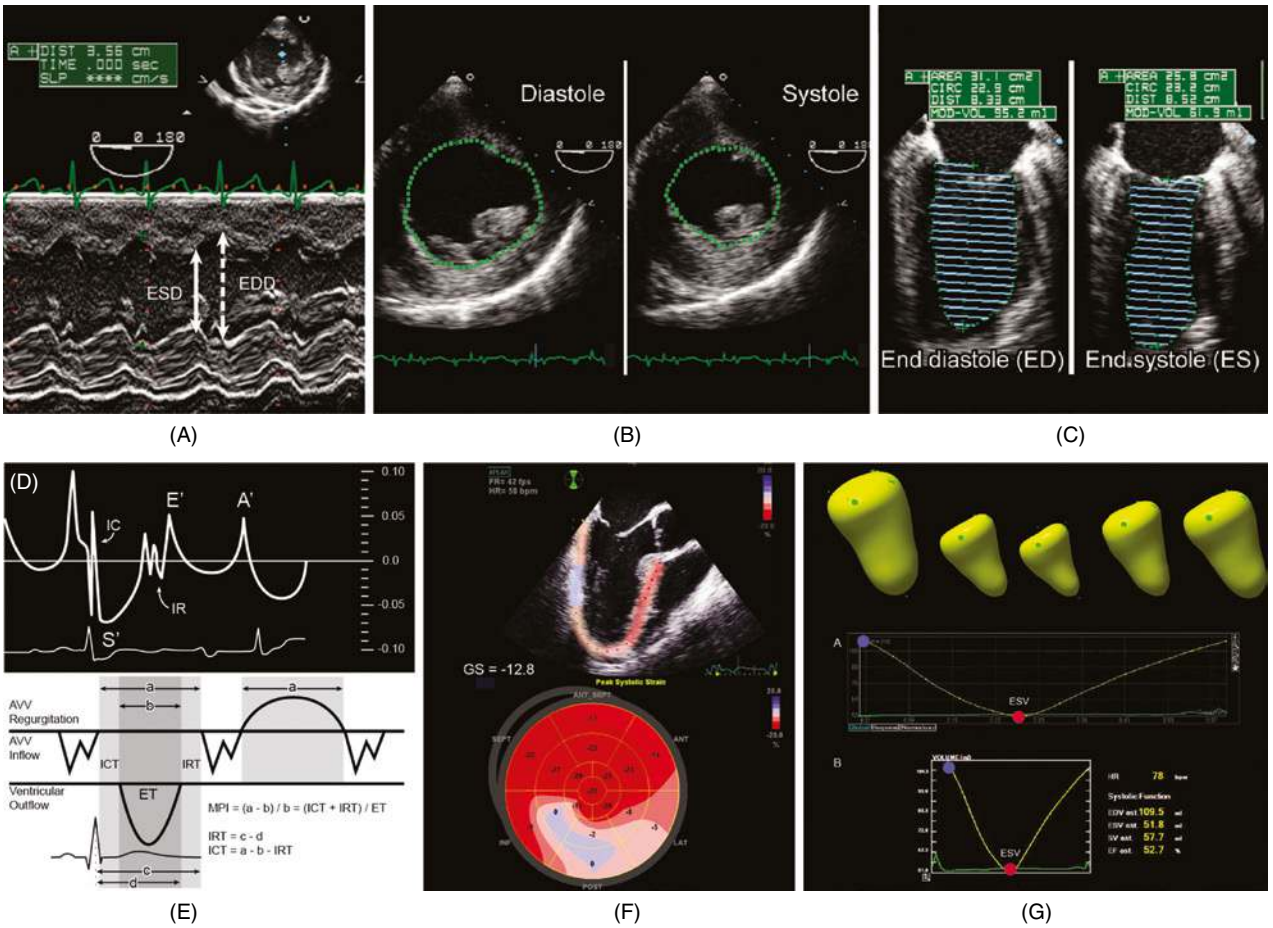


Figure 15.10 *Echocardiographic evaluation of left ventricular (LV) function*. This graphic displays the assessment of LV function using different techniques. (A) *Shortening fraction* estimates systolic function using linear measurements of LV end-diastolic (*EDD*) and end-systolic (*ESD*) chamber dimensions from a TG Mid Pap SAX view. (B) *Fractional area change* measures LV EDD and ESD chamber areas from a TG Mid Pap SAX view. (C) *Ejection fraction* measurement with Simpson's method of discs uses ME 4-Ch and/or ME 2-Ch views to trace the LV endocardium at *EDD* and *ESD*. Integrated machine software divides the LV into slices to calculate the volume. (Sources for A–C: Vegas [111, 112]. Reproduced with permission of Springer Nature.) (D) *Tissue Doppler imaging* of the lateral mitral valve annulus demonstrates a systolic velocity (*S'*) and two opposite-directed velocities, in early diastole (*E'*) and late diastole (*A'*) (graphic representation from a midesophageal window). The S' wave velocity provides an estimate of LV ejection fraction. *IC* isovolumetric contraction; *IR* isovolumetric relaxation. (E) *Myocardial performance index* is measured using spectral Doppler of the aortic outflow and mitral inflow as described in the text. (F) *Speckle tracking* can easily measure strain and strain rate (shown here for a ME LAX view) and peak systolic strain displayed in a bull's-eye format. (G) *3D assessment* of an endocardial cast derived from a 3D data set can be analyzed to estimate LV volumes and ejection fraction. (Source: Vegas [112]. Reproduced with permission of Springer Nature.) *ESV* end-systolic volume.

EF represents the most common measure of ventricular systolic function by echocardiography. The calculation of LVEF as a percentage (normal range: 56–78%) is as follows:

$$\text{LVEF}(\%) = \frac{(\text{LVEDV} - \text{LVESV}) \times 100}{\text{LVEDV}}$$

The end-diastolic volume (EDV) and end-systolic volume (ESV) of the LV can be determined by using 2D geometric methods and, more recently, from 3D volumes. The *Simpson method of discs* (MOD) in the ME 4-Ch and ME 2-Ch views (single or biplane method) divides the LV into slices of known thickness, whereby the sum of the slices represents the LV volume. The technique requires tracing the LV cavity at end diastole and end systole and determining the LV length through the apex (Figure 15.10C). The ultrasonography machine software automatically determines the LV volumes, SV, and LVEF.

A full volume data set acquired by 3D imaging can assess LV volume using two methods: 3D-guided biplane analysis and direct volumetric analysis. The 3D-guided biplane method minimizes foreshortening of the LV by positioning two perpendicular 2D planes accurately through the LV apex, thereby creating ideal ME 4-Ch and ME 2-Ch views. The LV volumes, LVEF, and mass are calculated by applying the modified Simpson biplane MOD. Direct volumetric analysis, performed with specialized software available on the ultrasonography system, measures LV volume throughout the cardiac cycle from a 3D surface-rendered cast of the LV cavity (Figure 15.10G). The software measures the EDV and ESV and calculates the SV and LVEF. This method accurately measures LV volumes, particularly in patients with an abnormal ventricular shape or regional wall motion abnormalities. The benefit of this analysis technique relates to better alignment of imaging planes through the cardiac apex, inclusion of more endocardial surface during

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the analysis, and the lack of geometric shape assumption. LV and RV volumes measured by 3D TTE are comparable to 2D TTE, CMR, and CT techniques. Assessing ventricular function with 3D technology is of great benefit in CHD, particularly in patients with single ventricle anatomic variants.

Doppler estimation of *SV and CO* uses the spectral Doppler mode. Any intracardiac site where recording both the cross-sectional area (CSA) and the flow velocity time integral (VTI) can be used to determine SV, as SV = CSA × VTI. An easy application of this method involves measuring the diameter of the AoV annulus (ME AoV LAX view) and flow through the valve (DTG 5-Ch view). Because the CSA of the AoV annulus does not usually change, serial monitoring of SV (and CO) mirrors changes in the VTI. The product of SV and heart rate represents the CO.

TDI records and displays pulsed-wave Doppler signals produced by the low-velocity movement of tissue. Positioning the sample volume at the lateral or septal mitral annulus measures and displays peak myocardial velocity (Figure 15.10D). Obtaining an optimal spectral trace depends on parallel Doppler alignment and tissue devoid of artifacts from reverberation, side lobes, or dropout. The TDI spectral display of the mitral annulus comprises a systolic velocity (S′) and two opposite-directed velocities recorded in early diastole (E′) and late diastole (A′). The S′ velocity is an estimate of LVEF, but not specifically a measure of contractility. Normal values for TDIs in pediatric and adult patients differ with heart rate, age, ventricular morphology, and loading conditions. These velocities are now routinely part of ventricular functional assessment by transthoracic imaging [109].

The *myocardial performance index (MPI)*, or *Tei index*, is a Doppler-derived measure of global ventricular function. It incorporates both systolic and diastolic time intervals and thus represents both systolic and diastolic performance [113]. The MPI is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ejection time (ET):

$$\text{MPI} = \frac{\text{ICT} + \text{IRT}}{\text{ET}}$$

The longer the isovolumic times, the higher the MPI and the worse the ventricular performance.

Pulsed-wave Doppler interrogation of the respective AV valve and outflow tract can easily measure components of the index for either the LV or the RV (Figure 15.10E). TDI derives the MPI over a single cardiac cycle, making it more accurate than the conventional Tei index. Studies have established normal MPI values for both adults and children (normal values in adults: LV, 0.39 ± 0.05 and RV, 0.28 ± 0.04; normal values in children: LV, 0.35 ± 0.03 and RV, 0.32 ± 0.03) [114, 115]. This index has been applied to the assessment of LV and RV function in patients with CHD, as well as to the evaluation of complex ventricular geometries [115–117]. It has also been used in the intraoperative setting to study the cardiovascular effects of anesthetic agents in children with CHD [118].

Strain and strain rate imaging are newer echocardiographic modalities that offer an enhanced approach to evaluating regional myocardial contraction and relaxation. During systole, the actual volume of myocardial tissue remains unchanged, but the myocardium changes in shape or deforms in three dimensions: longitudinal (shortening), radial (thickening), and circumferential (shortening and torsion). Strain and strain rate analyze ventricular deformation to quantify global and regional ventricular function more accurately than other functional indexes [104, 105, 110, 119–121]. Strain is a single, dimensionless (%) parameter that examines the motion deformation between two points in the myocardial wall. Total deformation in all dimensions represents a percentage change from the initial length. Negative strain implies that the fibers shorten (circumferential plus longitudinal) or thin (radial), whereas positive strain indicates that the fibers lengthen (circumferential plus longitudinal) or thicken (radial). End-systolic strain estimates LVEF. Strain rate is the speed of deformation or the change in strain over time (1/s). Peak systolic stain rate is a measure of contractility.

Two methods can assess myocardial deformation: TDI and speckle tracking. *Speckle tracking* of myocardium from a standard 2D image quantifies myocardial deformation without the limitations of angle dependence associated with TDI. Speckle tracking involves frame-by-frame analysis of the movement of a region of speckles of the myocardium to derive their direction and velocity (shift over time) of tissue movement relative to each other. Speckle tracking is less influenced by artifacts, although reverberations and dropout of myocardial tissue are problematic. Speckle tracking displays peak strain as an average value for each regional wall. Averaging these peak strain values provides the *global longitudinal peak systolic strain* (GLPSS), a measure of global systolic function. A colorized bull's-eye format displays the distribution of regional peak systolic and global systolic strain (Figure 15.10F). The analysis of myocardial deformation has been applied to various cardiovascular diseases, including cardiomyopathy, myocarditis, and valve pathology, among many other conditions. The use of TEE for this purpose has been extended to the perioperative setting, but experience with this application remains limited [106, 107].

Regional wall motion

Dividing the LV into segments better describes regional wall motion abnormalities and correlates them with coronary artery anatomy. Analysis of LV segmental function is based on a qualitative visual assessment for motion or thickening of a segment during systole. The ASE and SCA use a *17-segment LV model* that divides the basal and mid-levels into six segments each and the apex into four; the 17th segment is an apical cap (devoid of LV cavity) [99, 122]. TG SAX views show one LV level at a time, but these views have the advantage of simultaneously showing portions supplied by all major coronary arteries (right, left anterior descending, and circumflex vessels). Using other ME TEE views complements this assessment by showing additional LV wall segments (Figure 15.11).

Regional wall motion abnormalities detected by TEE in pediatric patients, like those in adult patients, have been considered markers of compromised myocardial blood flow [124, 125]. Segmental abnormalities can occur from surgical manipulations that alter coronary blood flow, either from coronary dissection, interventions involving the Ao or coronary arteries, intracoronary air, or localized reperfusion injury during cardiac surgery.

RV systolic function

The echocardiographic assessment of RV systolic function is complicated by the nongeometric, asymmetric, crescent shape of the ventricle, which precludes easy application of

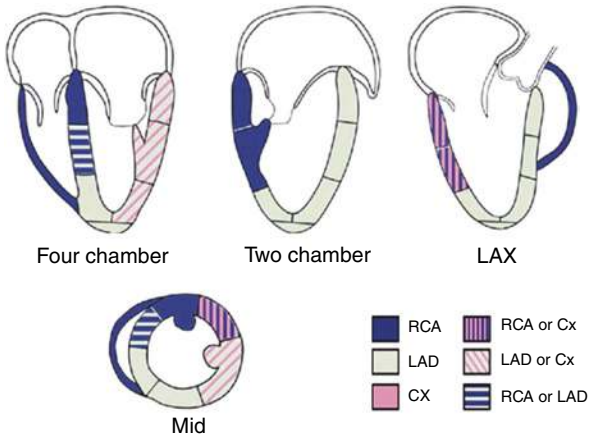


Figure 15.11 *Myocardial blood supply and corresponding TEE views.* The typical distributions of the right (*RCA*), left anterior descending (*LAD*), and circumflex (*CX*) coronary arteries as assessed by TEE imaging is shown. The coronary arterial distribution varies among patients. Some segments have variable coronary perfusion. (Source: Reeves et al. [123]. Reproduced with permission of Elsevier).

quantitative methods [126, 127]. Despite these challenges, several echocardiographic approaches can assess RV function [128–130]. The most commonly used of these approaches are *RV FAC* and *tricuspid annular plane systolic excursion (TAPSE)*. Tissue Doppler and strain echocardiography following the same principles described earlier can evaluate the RV as well as the LV [131]. Doppler measurement of the *RV myocardial performance index* (RV MPI) can augment the qualitative assessment of RV size and function. As previously mentioned, CMR is the current reference standard for assessing RV volume and systolic function.

The *RV FAC* is computed with a formula of area measurements like that for the LV FAC; these measurements are made by tracing the endocardial border of the RV during systole and diastole from the ME 4-Ch view. The normal range of values for RV FAC is 35–60%; values of 25–35% indicate mild dysfunction, 18–24% moderate dysfunction, and <17% severe dysfunction.

TAPSE is the distance of systolic excursion of the lateral tricuspid valve (TV) annulus in a longitudinal plane, often measured by using M-mode. It is a surrogate measure of global RV function (normal: 16–30 mm in adults) that correlates with angiography, biplane MOD, and FAC. Unlike TTE, TEE does not easily achieve parallel alignment in the ME 4-Ch view for this M-mode assessment; as an alternative, the TG RV Inflow view (a cross section included in the adult but not pediatric and congenital comprehensive TEE guidelines) may offer better alignment.

Evaluation of diastolic function

Diastolic dysfunction plays a major role in cardiovascular disease and is a risk factor for adverse clinical outcomes in all patients, including pediatric and adult patients with CHD [132]. The literature and ASE guidelines extensively detail the echocardiographic assessment of diastolic function [133–136]. The evaluation of LV diastolic function uses transmitral inflow Doppler indices (E, A, deceleration time) and tissue Doppler diastolic mitral annular velocities (E′, A′) at the lateral mitral annulus [137]. Combining these values, along with other Doppler echocardiographic variables (e.g., pulmonary venous flows), can classify patterns of diastolic dysfunction and assess disease progression. In a similar way, evaluating RV diastolic function involves TDI of tricuspid annular velocities.

Unfortunately, evaluating diastolic function in pediatric patients is complicated by the many confounding variables that influence Doppler assessment and interpretation of findings [138]. Although reports exist of the perioperative evaluation of diastolic function in adult patients undergoing cardiac surgery [137, 139–141], concerns remain about applying values derived from TTE performed in awake patients to TEE performed on patients under general anesthesia [142]. To the best of our knowledge, no formal studies have extensively explored diastolic function with TEE in children or, specifically, in the CHD population.

Hemodynamic evaluation

Echocardiography is an excellent noninvasive tool to obtain semiquantitative and quantitative hemodynamic information in CHD [143]. Doppler assesses blood flow and displays it as color superimposed over a 2D image (color Doppler) or as a spectral graph of velocity over time (spectral Doppler). Information obtained from Doppler can derive measures of pressure, volume, and flow [144].

Spectral Doppler measures the velocity of blood at a specific position, using a sample volume of *pulsed-wave Doppler* or along a sample line with *continuous-wave Doppler*. Doppler measurements require adequate alignment of spectral Doppler sampling to the direction of blood flow to minimize underestimation. Tracing the spectral Doppler display yields values for peak and mean velocities and the area under the curve (i.e., the flow VTI). The display of Doppler waveforms at a sweep speed of 100–150 mm/s can help identify temporal changes in the velocity flow profile, particularly in children with fast heart rates.

The complete *Bernoulli equation* is a complex formula that incorporates Doppler velocity measurements, flow acceleration, and viscous friction (blood viscosity) to estimate the *peak instantaneous pressure gradient* (PG) across an orifice. In clinical practice, a simplified version of the Bernoulli equation is sufficient in most cases to estimate the PG from the measured peak velocity (V) as follows:

$$\mathrm{PG}\,(\text{in mmHg}) \text{ or } \Delta P = 4V^2$$

Good correlation exists between Doppler estimates of PGs and direct pressure measurements. Preoperative PG estimates obtained when patients are awake or lightly sedated may differ from those obtained in the operating room under general anesthesia and conditions that may influence ventricular loading and systolic function.

No echocardiographic technique measures intracardiac pressures directly. Instead, it is necessary to use Doppler velocity measurements of regurgitant jets or across structures and apply the modified Bernoulli equation $\left(\Delta P = P_1 - P_2 = 4\left(V_2^2 - V_1^2\right)\right)$ to determine the pressure drop or gradient. In most cases, V_2 is much higher than V_1, so one can usually neglect the V_1 component of this equation. This technique is particularly valuable for estimating RV systolic pressure (RVSP), which should reflect the PA systolic pressure (PASP) in the absence of obstruction to RV outflow and which can be used to identify pulmonary hypertension. Estimating RVSP uses measurements of the peak

velocity of the tricuspid regurgitant (V_{TR}) jet along with an estimate of right atrial pressure (RAP) in the following equation:

$$\text{RVSP (in mmHg)} = 4V^2_{TR} + \text{RAP}$$

Color Doppler facilitates the detection of abnormal flows and, along with other parameters, can assess disease severity (Table 15.8). Measurements of the jet area, vena contracta, and the region of flow acceleration can be combined to grade the severity of regurgitant valvular lesions [145–147]. In the operative setting, however, most of this evaluation is qualitative.

Shunt fractions can be calculated by measuring flow (Q) through the pulmonary (Qp) and systemic (Qs) circulations. Typically, measurement of flow is across the PV and AoV from the Doppler-derived VTI and the CSA of each arterial root as:

$$Q = \text{VTI} \times \text{CSA}$$

TEE is a reliable monitor of LV filling (preload) changes in all age groups. In pediatric patients, experienced echocardiographers can identify with high sensitivity and specificity mild reductions in blood volume by changes in LVEDA by using TEE in the TG Mid Pap SAX view [148]. A marked decrease in both EDA and ESA suggests hypovolemia. Patients with conditions such as arterial vasodilatation, severe aortic regurgitation, mitral regurgitation, and VSD may have a reduced ESA but typically have a normal-to-increased EDA in this TEE view.

KEY POINTS: TEE EXAMINATION IN CHD

- TEE plays a critical role in CHD not only in characterizing the structural abnormalities but also in the functional and hemodynamic evaluation.
- The TEE examination in CHD requires navigating different windows in the esophagus and stomach to obtain cross-sectional images of structures in multiple planes.
- The examination in children and all patients with CHD should include, in most cases, the 28 views suggested in the TEE guidelines addressing these patient populations and additional modified planes as necessary.
- There is no specific recommended sequence for the TEE examination in the patient with CHD.
- In addition to the interrogation in specific 2D views, the comprehensive examination in the patient with CHD requires the use of sweeps between various planes to allow a 3D reconstruction of the anatomy and related abnormalities by the examiner.
- 3D TEE provides more information about cardiac anatomy and spatial relationships than 2D TEE; however, the size of the current adult devices limits their use to older children.
- Benefits of the real-time 3D TEE technology include the ability to freely rotate a volume-rendered 3D object in the display to be viewed from any orientation with the possibility for dissection to provide detailed information.

Table 15.8 Doppler parameters in severe valvular disease (Adult Values)

	Aortic	Mitral	Tricuspid	Pulmonic
Severe regurgitation				
CW Doppler signal strength	Dense	Dense	Dense	Dense
JA mapping (cm^2) or JA/LVOT area (%)*	>60	>10	>10	
JA/atrial area or JH/LVOT height (%)**	>65	>40		Large
Doppler flow reversal	Desc aorta	S pulmonary vein	S hepatic vein	PA
Regurgitant volume (ml)	≥60	≥60	≥60	≥60
Regurgitant fraction (%)	≥50	≥50	≥50	≥50
Vena contracta width (mm)[a]	6	≥7	>7	
Effective regurgitant orifice area (cm^2)	≥0.30	≥0.4	≥0.4	
PISA radius (mm)[b]		>10	>9	
PHT (ms)	<200–300			
Severe stenosis				
Velocity (m/s)	>4	>3	>1.5	>4
Mean pressure gradient (mmHg)	>40	>10	>5	See note
Valve area (cm^2)	<1	<1	<1	<0.5
PHT (ms)		>220	>195	

The severity of valve regurgitation or stenosis can be assessed by using different spectral and color Doppler modalities. Adult values for severe disease of different cardiac valves are shown. *Valvular regurgitation*: color Doppler can be used to map the area of a regurgitant jet, measure the vena contracta or narrowest region of the regurgitant jet (corresponds to the diameter of the regurgitant orifice area), and determine the PISA radius (based on the principle of a flow convergence zone corresponding to regurgitant flow). Spectral Doppler of the regurgitant jet signal strength by CW, systolic flow reversal in major vessels, and PHT (time needed for the peak transvalvular pressure gradient to fall to half its value) can be evaluated to assess severity. The regurgitant volume, fraction, and effective regurgitant orifice area can be calculated. *Valvular stenosis*: spectral Doppler allows assessment of velocity and pressure gradient, calculation of valve area, and measurement of PHT. *CW* continuous-wave; *desc* descending; *JA* jet area; *JH* jet height; *LVOT* left ventricular outflow tract; *PA* pulmonary artery; *PISA* proximal iso-velocity surface area; *PHT* pressure half-time. Note: For the pulmonic (pulmonary) valve, peak pressure gradient (mmHg) >64.

Nyquist limits:

[a] 50–60 cm/s

[b] 40 cm/s

* JA mapping (cm^2) applies to the mitral and tricuspid valves and JA/LVOT area (%) to the aortic valve.

** JA/atrial area applies to the mitral valve and JH/LVOT height (%) to the aortic valve

Applications of TEE in CHD

Intraoperative setting

The benefits of using TEE during surgery for CHD include monitoring, assessing the adequacy of cardiac de-airing, detecting complications, and guiding the placement of intravascular or intracardiac catheters [149–151]. TEE also influences anesthetic management in CHD by guiding changes in inotropic strategy and volume replacement [152, 153].

Intraoperative TEE influences surgical management in 3–15% of cases; the results alter the preoperative diagnosis in 3–5% of cases and prompt a return to CPB in 3–7% [153–155]. A report on intraoperative TEE during congenital heart surgery in a wide range of patients (aged 2 days to 85 years) stated that using TEE resulted in major changes to treatment in 13.8% of the patients [156]. These changes were most frequent during reoperations, valve repairs, and complex outflow tract reconstructions.

A critical role of intraoperative TEE is assessing the adequacy of the surgical intervention and detecting residual abnormalities that may require immediate revision [29, 157–163]. This feature represents a major benefit of intraoperative TEE, as it can positively influence clinical patient outcomes. In return-to-CPB situations, factors such as the level of inotropic support, loading conditions of the ventricle, and myocardial function can influence the echocardiographic findings, potentially underestimating or overestimating the hemodynamic severity of the condition. Consequently, decisions regarding return to CPB should be interpreted in this context and in consideration of the overall risk-to-benefit ratio.

In a study of TEE in 230 patients, detecting and surgically revising residual abnormalities improved outcomes, whereas the patient's course was suboptimal if the residual defect remained [161]. In addition to the patient benefits afforded by this imaging modality, routine TEE during congenital and pediatric heart surgery appears to be cost-effective [164, 165]. The experience regarding the value of intraoperative TEE has been so compelling that, at many centers, it has become the standard of care.

Cardiac catheterization laboratory

During the past several decades, transcatheter-based therapies and interventional procedures have become increasingly used in the nonsurgical management of congenital cardiovascular anomalies. Many of these approaches have extended from the cardiac catheterization laboratory to the operating room (and vice versa) as combined efforts of interventional cardiologists and cardiothoracic surgeons. TEE allows safer and more effective application of these interventions by decreasing radiation exposure, reducing the amount of contrast agents administered, and limiting the duration of the procedure [166]. As with intraoperative TEE, major benefits include acquisition of detailed anatomic and hemodynamic data before and during the procedure; real-time evaluation of catheter and device placement across structures while assisting in procedural guidance; immediate assessment of the intervention; and monitoring for procedural complications. The high success rate and low incidence of complications with these procedures are a testament to the refinement of interventional techniques coupled with advances in TEE [21].

Intensive care unit

Echocardiography remains an important diagnostic tool in the ICU to manage postoperative cardiac surgical patients [167]. Bandages, chest tubes, mediastinal air, positive pressure ventilation, and even an open sternum frequently render TTE imaging challenging and, at times, infeasible. Thus, alternate imaging approaches such as TEE or, at times, epicardial imaging in patients with an open sternum may be the preferred imaging modality to address important clinical questions, particularly in ventilated patients [48, 168]. In the hemodynamically unstable patient in the ICU, TEE can help identify problems related to preload, myocardial function, afterload, and cardiac tamponade. In the absence of the classic clinical finding of tamponade, TEE can diagnose localized cardiac compression from a loculated collection or even "dry" tamponade. New findings related to outflow tract obstruction, significant native or prosthetic valve dysfunction, or regional wall motion abnormalities may prompt surgical reintervention. Additional applications of TEE in the ICU include investigating possible occult shunts, evaluating mechanical circulatory support devices, and facilitating support weaning.

KEY POINTS: APPLICATIONS OF TEE IN CHD

- For CHD patients, TEE is most likely to be used in the operating room, cardiac catheterization or electrophysiology laboratory, and critical care setting.
- Preoperative TEE permits the baseline evaluation of anomalies, confirms preoperative diagnoses, identifies new or different pathology, excludes defects, and refines the surgical and anesthetic plans.
- Major roles of postoperative TEE include assessing the adequacy of the intervention, guiding the revision of the repair if necessary, and identifying problems associated with weaning from CPB.
- Several factors can influence the echocardiographic findings, potentially underestimating or overestimating the severity of the condition, which warrants their consideration in return-to-CPB decisions.
- TEE facilitates procedures in the catheterization or electrophysiology laboratory, may enhance their safety, and limits the duration of the intervention.
- In the ICU, TEE can address important clinical questions when other imaging modalities cannot be used or cannot provide the required information; in the hemodynamically unstable patient, TEE can help identify the cause of the instability.

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TEE safety and complications

Although complications related to transesophageal instrumentation occur at a rate of 1–3%, extensive clinical experience indicates that serious TEE complications are rare [169–172]. Probe manipulation can affect hemodynamic and respiratory parameters; this requires attentiveness, particularly in small infants [173, 174]. Aortic compression can influence blood pressure readings, depending on the location of the arterial monitoring line.

In the patient with an aberrant origin of a subclavian artery with a retroesophageal course, the arterial pressure monitoring line should be placed in an extremity not supplied by the anomalous vessel, as the pressure tracing may be lost with insertion or manipulation of the TEE probe. This occurs because the probe compresses the vessel as it courses behind the esophagus. In fact, placing a TEE probe occasionally detects this vascular anomaly [175, 176]. TEE is of little benefit in the surgical management of isolated vascular malformations, such as vascular rings, and it may in fact be risky, as probe insertion can significantly compromise respiratory function [177]. In infants with anomalous pulmonary venous connections, compression of a posteriorly located pulmonary venous confluence by the TEE probe can cause detrimental hemodynamic effects (Figure 15.12) [54]. In such patients, inserting the TEE probe after sternotomy may be safer [178].

Respiratory compromise can result from displacement of the ETT or accidental extubation. Capnography can help identify these complications. If desaturation occurs acutely, the position of the TEE probe tip should be immediately adjusted to neutral, and the position of the ETT should be checked. During removal of the TEE probe, holding the ETT firmly prevents inadvertent extubation. Airway compression during manipulation of the imaging probe can also result in ventilatory difficulties.

TEE can cause dysphagia, resulting from mild mucosal injury detectable by flexible esophagoscopy in some patients [179–181]. Unrecognized esophageal perforation during intraoperative TEE has been reported in a small infant [182]. Inadvertent laceration of the stomach has been described from the surgical incision extending into the xyphoid region, while the abdominal wall protruded anteriorly during TG imaging [169]. These cases underscore the need to exercise meticulous care during the insertion and manipulation of TEE probes, particularly in the critically ill neonate.

Endocarditis has been temporally related to TEE examination. However, the incidence of positive bacterial blood cultures immediately after TEE is extremely low and within the expected rate of false-positive results. The American Heart Association guidelines do not recommend administering antibiotics solely to prevent endocarditis in patients who undergo gastrointestinal tract procedures, which would include TEE [183].

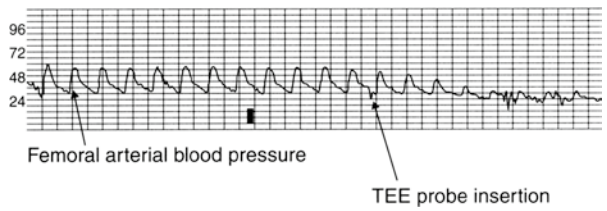


Figure 15.12 *Hemodynamic changes related to TEE probe.* The figure displays an acute decrease in systemic arterial blood pressure, as recorded from a femoral arterial line, related to TEE probe insertion in a neonate with total anomalous pulmonary venous return. The hypotension was likely the result of probe compression of the pulmonary venous confluence.

KEY POINTS: TEE SAFETY AND COMPLICATIONS

- Serious complications related to TEE have been reported, but these are fortunately rare.
- Infants are at elevated risk of TEE complications, including respiratory and hemodynamic compromise.
- Anomalies such as vascular rings and anomalous pulmonary venous drainage may preclude TEE imaging.
- When TEE imaging is planned, the ETT should be well secured to prevent dislodgement or inadvertent tracheal extubation.
- A low threshold to adjust the TEE probe position, pause or discontinue imaging, or remove the device is warranted in cases of acute arterial desaturation or potentially adverse hemodynamic changes.

Evaluation of selected congenital heart defects before and after intervention

In the perioperative setting, echocardiographic assessment during the pre-CPB period confirms the presence of the operative lesion(s), documents associated findings, and assesses cardiac function. Post-CPB evaluation focuses on determining the adequacy of the repair, mainly by identifying residual intracardiac shunts, outflow tract obstructions, and valvular regurgitation and by assessing ventricular performance [159, 161, 184]. Numerous educational resources provide comprehensive reviews on TEE imaging and hemodynamic assessment in CHD [28, 80, 184–186]. The following sections present an overview of pertinent TEE findings in selected anomalies and a summary of relevant aspects of the pre- and post-CPB examination (Table 15.9). The reader should refer to other chapters throughout this textbook that address in further detail each of the highlighted congenital lesions which follow.

Table 15.9 Transesophageal echocardiography examination (TEE) in selected congenital heart defects

	Pre–cardiopulmonary bypass TEE	Post–cardiopulmonary bypass TEE
Aortic stenosis	• Define aortic valve anatomy • Evaluate location (subvalvular, valvular, supravalvular) and severity of the obstruction • Characterize the pathology • Evaluate for aortic regurgitation • Determine presence of LV hypertrophy and assess function	• Assess for residual outflow obstruction • Evaluate for aortic regurgitation • Examine for the presence of new VSD • Examine for mitral regurgitation • Assess ventricular function • Evaluate prosthetic valve function (if applicable) • After a Ross procedure, assess autograft and RV-to-PA conduit

Atrial septal defect (ASD)	• Define location and size of defect
	• Examine defect rims for catheter-based interventions
	• Assess AVV regurgitation
	• Determine RA and RV sizes
	• Assess baseline ventricular function
	• Estimate RVSP (PASP) from TR jet velocity
	• Identify associated anomalies
	  ○ MV prolapse
	  ○ Cleft AVV
	  ○ Partial anomalous venous drainage
		After repair of all ASDs:
		• Assess for residual shunting
		• Evaluate ventricular function
		After repair of secundum and primum defect:
		• Examine for AVV regurgitation
		After repair of sinus venosus defect:
		• Evaluate for SVC obstruction
		• Assess for pulmonary venous obstruction (if associated anomalous pulmonary venous return)

Atrioventricular septal defect (AVSD)	• Define location, size, and type of defects
	• Characterize shunting across defects
	• Evaluate for additional septal defects
	• Assess AVVs
	  ○ Rastelli type in complete defect
	  ○ AVV regurgitation
	  ○ Relation of valvular structures to ventricles
	  ○ Balanced vs. dominant type
	  ○ Valvular support apparatus
	• Interrogate ventricular outflows (obstruction)
	• Assess baseline ventricular function
	• Estimate RVSP/PASP
		After repair of all AVSDs:
		• Assess for residual shunts
		• Evaluate for LVOT obstruction
		• Evaluate ventricular function
		After repair of partial AVSD/cleft MV closure:
		• Evaluate for residual or new AVV regurgitation (mild regurgitation may be acceptable)
		• Examine for mitral inflow obstruction (if mitral cleft closed)
		After repair of complete AVSD:
		• Examine for AVV stenosis (particularly if annuloplasty or left-sided cleft closure performed) and regurgitation

Congenitally corrected transposition (L-TGA)	• Confirm anatomy • Confirm AV and ventriculoarterial relationships • Evaluate AVV function • Assess ventricular sizes and function	• Assess for AVV regurgitation • Examine outflow tracts for patency/obstruction • Determine adequacy of the intervention (PA banding, classic repair, or double switch operation) • Assess ventricular function
Double-outlet right ventricle	• Evaluate septal defects (size, location, shunt direction) • Assess relation of VSD to great arteries • Assess physiology from anatomic findings (i.e., VSD, transposition or Taussig-Bing, tetralogy type) • Determine great artery relationship (normal, malposed) • Evaluate for outflow tract obstruction • Evaluate ventricular sizes and function • Evaluate associated defects	• Evaluate for residual intracardiac shunts • Assess for outflow tract obstruction • Examine AVVs and semilunar valves for regurgitation/stenosis • Depending on the procedure interrogate LV-to-Ao baffle and RV-to-PA conduit function as applicable • Assess ventricular function
Pulmonary stenosis	• Define pulmonary valve anatomy • Evaluate location (subvalvular, valvular, supravalvular) and severity of the obstruction • Characterize the nature of the pathology • Determine size of the PAs • Evaluate for intracardiac shunts • Evaluate for RV hypertrophy and function	• Examine for residual outflow obstruction • Assess for pulmonary regurgitation • Investigate for new VSD • Examine for TR • Assess ventricular function • Assess conduit or prosthetic valve function as applicable

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Table 15.9 (Continued)

	Pre–cardiopulmonary bypass TEE	Post–cardiopulmonary bypass TEE
Tetralogy of Fallot	• Define size and location of septal defects • Examine for additional VSDs or associated anomalies • Evaluate RVOT (subvalvular, valvular, supravalvular regions) ○ Define morphology, obstruction, gradients • Determine size of pulmonary arteries • Assess Ao override/ root size, AoV competence • Identify origin and course of coronary arteries • Evaluate baseline ventricular function	• Evaluate for residual VSD • Assess RVOT velocity/gradient • If there is residual obstruction, define type (fixed vs. dynamic) and severity • Evaluate for pulmonary regurgitation • Estimate RVSP (from TR jet) • Evaluate RV and LV function • Examine conduit or prosthetic valve function in pulmonary position
Transposition of great arteries (D-TGA)	• Confirm anatomy and ventriculoarterial relationships • Assess intracardiac shunts (location, size, flow direction, relation to outflows) • Assess for outflow tract obstruction • Evaluate AVVs and semilunar valves • Identify origin and course of the coronary arteries • Assess ventricular sizes and function • Assess septal geometry (indicator of ventricular pressures)	*After the arterial switch operation (Jatene procedure):* • Interrogate the neoaortic and pulmonary anastomoses (for stenosis) • Evaluate for semilunar valve competence • Assess patency of outflow tracts • Assess for AVV regurgitation • Evaluate for residual intracardiac shunts • Examine coronary blood flow • Assess global and segmental LV function
Truncus arteriosus	• Assess the truncal valve (for morphology, stenosis, and regurgitation) • Identify septal defects (size, location) • Determine the origin of the pulmonary arteries ○ Type of truncus ○ Pulmonary blood flow • Assess ventricular function	• Examine the truncal (aortic valve) for stenosis and regurgitation • Evaluate the RV-to-PA conduit (for stenosis or regurgitation) • Evaluate for residual VSD shunting • Assess for AVV regurgitation • Estimate RVSP (PASP) from TR jet • Assess ventricular function, including segmental wall motion (coronary arteries)
Single ventricle	• Evaluate morphologic type • Assess AVVs and semilunar valves, inflows, and outflows • Assess adequacy of the interatrial communication • Evaluate prior surgical interventions • Assess ventricular function	*After Fontan or Glenn procedure:* • Flow in Fontan or Glenn connections • Evaluate Fontan fenestration, if performed • AVV regurgitation • Atrial septal shunting for evidence of obstruction (if stenosis or atresia of AVV) • Assess ventricular function
Ventricular septal defect (VSD)	• Determine location and size of defect(s) • Evaluate for additional intracardiac shunts • Investigate for associated pathology: ○ AVV regurgitation ○ Aortic valve cusp herniation or prolapse ○ Aortic regurgitation ○ Subaortic membrane ○ Pulmonary valve stenosis ○ Double-chamber RV • Assess baseline ventricular function • Estimate RVSP (PASP) from TR jet or VSD peak velocity	*After repair of all VSDs:* • Evaluate for residual shunting (tiny patch leaks are acceptable) • Estimate RVSP from TR jet • Assess ventricular function *After repair of perimembranous defect:* • Evaluate for AVV regurgitation (TR in particular) • Assess for aortic regurgitation *After repair of supracristal (subarterial, doubly committed) defect:* • Evaluate for new aortic regurgitation • Evaluate for pulmonary regurgitation *After repair of muscular or inlet defect:* • Evaluate for AVV regurgitation

Abbreviations: *Ao* aorta; *AoV* aortic valve; *AV* atrioventricular; *AVV* atrioventricular valve; *LV* left ventricle; *LVOT* left ventricular outflow tract; *MV* mitral valve; *PA* pulmonary artery; *PASP* pulmonary artery systolic pressure; *RA* right atrium; *RV* right ventricle; *RVOT* right ventricular outflow tract; *RVSP* right ventricular systolic pressure; *SVC* superior vena cava; *TR* tricuspid regurgitation

Atrial septal defects

Anatomic and physiologic features

Interatrial communications allow blood to flow between the atria. By definition, a true ASD is a gap in the IAS tissue that permits shunting of blood between the atrial chambers. Other types of atrial communication do not necessarily result from a deficiency of IAS tissue. Typically, ASDs are classified into four types, although not all represent a "true" ASD. The defect location defines each type, which may be associated with other cardiac anomalies.

An *ostium secundum defect* (80% of ASDs) is a tissue defect that arises at or near the center of the IAS in the region of the fossa ovalis (septum primum). The defect usually has a complete surrounding rim of septal tissue, although portions of the tissue rim(s) are deficient in some cases. A secundum ASD can coexist with other congenital heart lesions and, in 30% of cases, with MV prolapse. An *ostium primum defect* (15% of ASDs) is a tissue defect in the inferior aspect of the IAS near the AV valves and is part of the spectrum of atrioventricular septal defects (AVSDs). The *sinus venosus defect* (5% of ASDs) is a tissue deficiency in the sinus venosus septum that occurs near the caval veins (superior vena cava and inferior vena cava [IVC] types). Sinus venosus defects are associated with partial anomalous pulmonary venous connection (PAPVC) or drainage. A *coronary sinus defect* is a rare atrial communication that frequently includes the coronary sinus orifice. This defect is a deficiency in the common wall that separates the coronary sinus from the LA. Left-to-right shunting occurs most commonly from the LA to the right atrium (RA) through the partially or completely unroofed coronary sinus, but the direction of shunting may be variable as influenced by atrial hemodynamics. These defects are frequently associated with persistent drainage of a left-sided SVC (LSVC) into the coronary sinus. A *PFO* represents a flap that arises from failure of the septum primum to adhere to the limbus of the septum secundum. There is no deficiency in septal tissue, though this interatrial communication can cause shunting under certain conditions.

The clinical manifestations of an ASD primarily relate to the magnitude of atrial-level shunting, which depends on the defect size, ventricular compliances, and PA pressures. An ASD, particularly a small defect, may represent an incidental finding on echocardiography. A large defect causes pulmonary overcirculation that results in symptoms of right-sided volume overload. Over time, atrial arrhythmias and heart failure can develop. Although older patients can have evidence of elevated PASP, they rarely have severe pulmonary hypertension.

Highlights of the TEE examination

Multiple ME views are necessary to completely assess the relatively thin IAS [187]. The perpendicular alignment of the imaging plane in the ME Bicaval view most reliably images the IAS. In the ME 4-Ch view, the imaging plane is parallel to the IAS; hence, a false "absence of tissue" may occur from dropout. Other helpful views include the DTG Atr Sept view. Measuring the gap in the septal tissue determines the size of the atrial communication. Communications at the atrial level as displayed by TEE appear in Figure 15.13.

Color and spectral Doppler interrogation can easily detect abnormal blood flow across the IAS. Left-to-right shunting is usual in an isolated ASD, but it may be right-to-left or bidirectional in patients with certain conditions (e.g., pulmonary hypertension) or coexistent defects. The peak velocity across the defect is inversely proportional to the defect's size, with a larger defect having lower velocity laminar flow. If there is a tricuspid regurgitation (TR) jet, it can estimate the PASP, as previously discussed.

TEE with saline contrast is the most sensitive method to detect interatrial shunts that are not evident by 2D or Doppler techniques. A contrast study involves vigorously agitating saline (3–10 mL) with <1 mL of air and injecting it rapidly into a central or arm vein. A better alternative may be aspirating the patient's blood and mixing it with saline or albumin. A negative study reveals no flow of bubbles across the IAS. A positive study indicates right-to-left shunting, with microbubbles present in the LA within five heartbeats of injection. A false-positive study can result from pulmonary arteriovenous malformations. Additionally, the appearance of noncontrasted blood in the contrast-filled RA can help identify left-to-right shunting. Saline contrast improves PFO detection, both at rest and with raised RAP [188]. A Valsalva maneuver can enhance the recognition of a small or intermittent right-to-left interatrial shunt. In the intubated patient, sustained lung inflation to a positive inspiratory pressure of about 25 mmHg for approximately 10 seconds can simulate a Valsalva maneuver.

The *preoperative TEE* examination for an ASD should confirm the location of the defect, its size, and the direction of the shunt. Guided by the specific type of defect, the TEE study should evaluate for existing or potential MV prolapse (secundum defect), cleft MV (primum defect), PAPVC (sinus venosus defect), and LSVC-to-coronary sinus connection (coronary sinus defect). Additional aspects of the TEE study in all defects include evaluating AV valve competence, associated anomalies, and ventricular function. Atrial communications with significant left-to-right shunting can cause right atrial and RV enlargement and diastolic flattening with paradoxical motion of the interventricular septum (IVS). The *postsurgical TEE* examination should evaluate the IAS for residual shunting, valvular competence, ventricular function, and flow across the systemic and pulmonary veins, depending on the defect and the type of intervention undertaken.

Transcatheter closure with an occluding device may be an option for selected secundum defects [19]. TEE assists in patient selection, procedural guidance, and immediate assessment of success and complications. Essential components of the TEE examination that contribute importantly to decision-making include determining the size and location of the defect, characterizing the orifice (single vs. multiple), evaluating the dimensions and adequacy of septal rims, and assessing the relationship of the defect to surrounding structures [189–193]. Advocates suggest routinely using 3D TEE during transcatheter closure when the patient's size allows it.

Postdeployment TEE assesses the device (integrity, position, and stability) and possible residual shunt, and identifies complications (Figure 15.14) [19, 194]. Placing a device can affect surrounding structures, resulting in compromised inflow from the caval veins, coronary sinus, or pulmonary veins; interference with valve function; and pericardial effusion.

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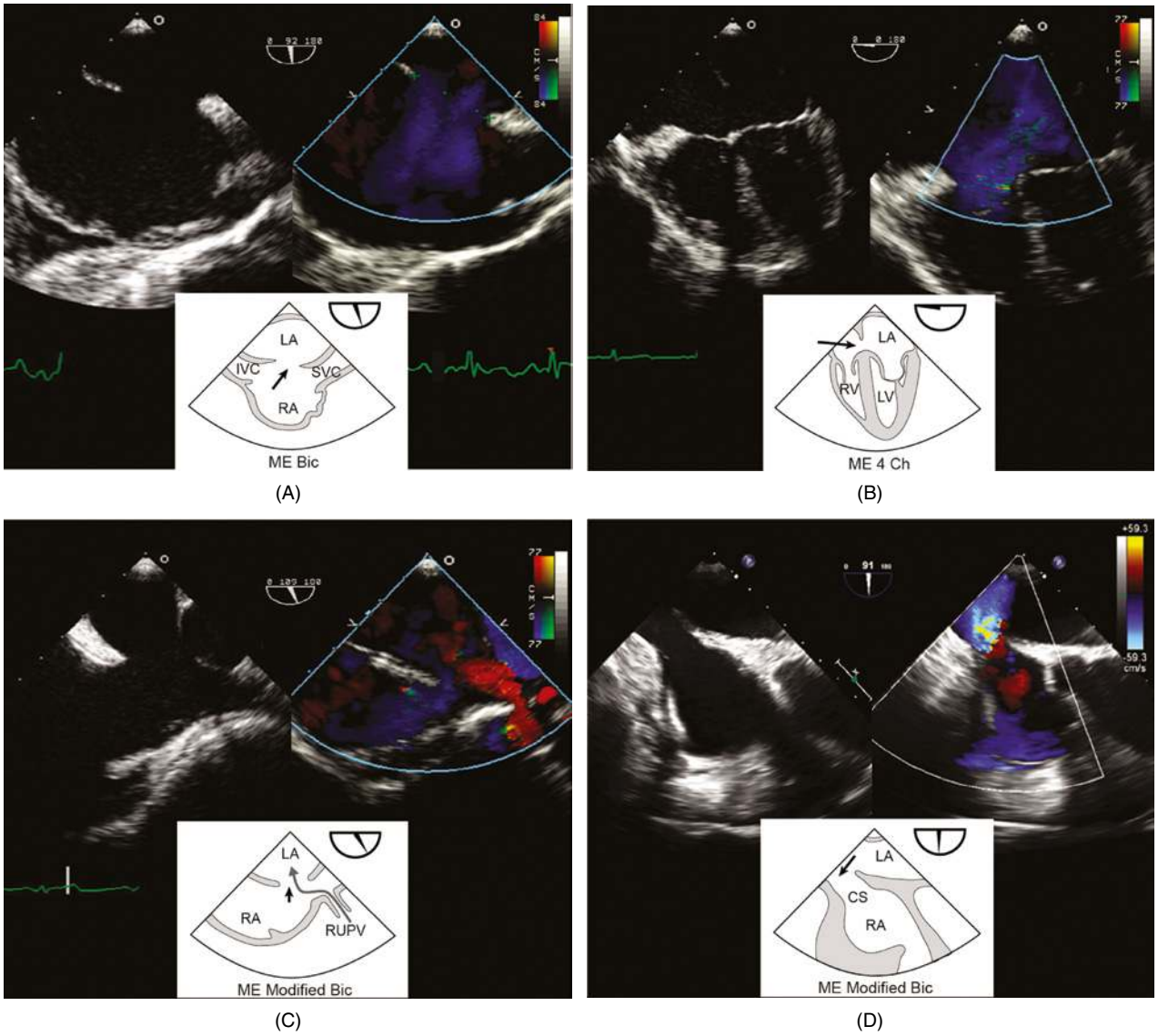


Figure 15.13 *Atrial septal defects (ASDs)*. (A) *Secundum ASD*. ME Bic view depicts a centrally located septal deficiency in this defect within the region of the fossa ovalis (*arrow*) and adjacent interatrial septal (IAS) rims. Comprehensive septal rim assessment requires multiple views. (B) *Ostium primum ASD*. ME 4-Ch view shows the inferior communication in the IAS in this defect (*arrow*). Note insertion of both atrioventricular valves (AVVs) into the interventricular septum at the same level. A cleft or commissure in the anterior mitral valve leaflet, also referred to as zone of apposition of the left AVV, is best seen in the TG Basal SAX view. The assessment of mitral regurgitation can be performed in the ME 4-Ch, ME 2-Ch, ME Mitral Comm, and ME LAX views. Mitral valve chordal attachments to the interventricular septum, when present, can be defined in the ME 5-Ch, ME LAX, TG LAX, and DTG 5-Ch views and assessed for related left ventricular (*LV*) outflow tract obstruction. (Source: Vegas [112]. Reproduced with permission of Springer Nature.) (C) *Sinus venosus ASD*. The ME Bic or modified views with slight probe withdrawal optimally images the superior type of defect (*small arrow*) and the superior vena cava (*SVC*) as it drains into the right atrium (*RA*). Anomalous drainage of the right upper pulmonary vein (*RUPV*) in the SVC-type defect (*long arrow*) results from unroofing of the wall that separates the RUPV from the left atrium (*LA*) as shown by color Doppler of pulmonary venous flow. Advancing the probe to the TG IVC/Hep Veins view in an inferior defect displays the atrial communication and region where the inferior vena cava (*IVC*) joins the RA. (D) *Coronary sinus ASD*. The examination of the coronary sinus (*CS*) is optimal in views that display this structure in both its long and short axes. A dilated CS is best imaged by probe retroflexion in the ME 4-Ch view or slight advancement towards the lower esophagus. Unroofing of the CS in this defect is demonstrated by echo dropout in the wall that separates the LA from the CS in the ME (4-Ch, 2-Ch, MV Comm, and LAX) views. Probe angulation between 90° and 120° assisted by color-flow Doppler in a modified ME Bic view depicts the defect and flow from the CS into the RA in the inferior portion of the atrium (*arrow*) as shown. A persistent left SVC, if present, appears in the ME MV Comm view as a wedge-shaped echo-free space between the left upper pulmonary vein and left atrial appendage or at the level of the AV junction in the ME 4-Ch and ME 2-Ch views. *RV* right ventricle. Diagrams courtesy of Ms. Willa Bradshaw.

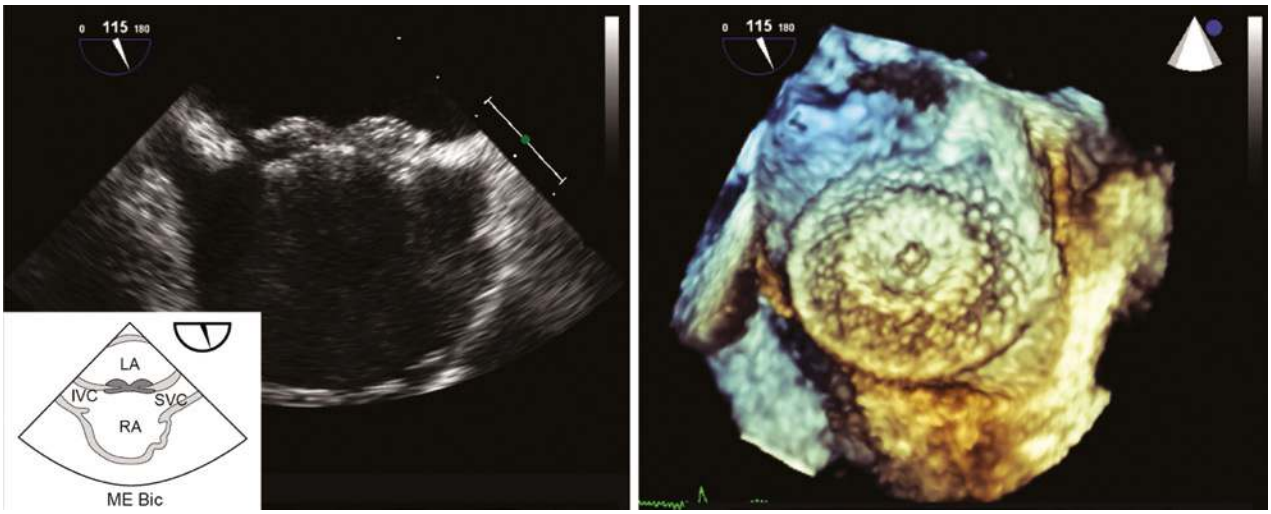


Figure 15.14 *Device occlusion of secundum atrial septal defect (ASD).* (A) ME Bic view depicts an Amplatzer™ ASD occluder device well positioned across the interatrial septum. (B) 3D TEE view from the right atrium (*RA*) depicts the details of the device in an *en face* perspective. *IVC* inferior vena cava; *LA* left atrium; *SVC* superior vena cava. (Source: Vegas et al. [41]. Reproduced with permission of Springer Nature.) Diagram courtesy of Ms. Willa Bradshaw.

Ventricular septal defects

Anatomic and physiologic features

The ventricular septum is a complex 3D structure formed by morphologically distinct subunits that can have tissue deficiencies that result in defects. The categorization of VSDs has been the subject of ongoing debate [195]. In this chapter, we use the classification scheme based on the location of the defect within the ventricular septum as follows: membranous, muscular, inlet, or subarterial. *A perimembranous defect* (70% of VSDs), also referred to as membranous, paramembranous, conoventricular, or infracristal, involves the thin membranous portion of the IVS adjacent to the TV and AoV. *A muscular defect* (20% of VSDs) can occur anywhere in the trabecular septum (mid, apical, anterior, and posterior regions) and is bound entirely by muscle. Single or multiple defects can be present. An *inlet defect* (5% of VSDs), also referred to as the "canal type of defect," results from incomplete formation of the central fibrous body or AV canal septum (see AVSD below). This communication is located at the crux of the heart, adjacent to the MV and TV annuli. An *outlet defect* (5% of VSDs), also described as infundibular, conal, subpulmonary, supracristal, doubly committed, or subarterial, occurs in the muscular portion of the septum that separates the outflow tracts. The various types of VSDs frequently overlap, as they can extend from one primary region to another. Associated lesions are identified in some cases, including patent ductus arteriosus (PDA; 6%) and coarctation of the Ao (CoA; 5–10%).

Highlights of the TEE examination

Systematically interrogating the entire IVS requires multiple TEE views [196]. The use of 2D imaging can identify each type of VSD (Figure 15.15), although small defects may require superimposed color Doppler to define their location and optimize spectral Doppler alignment. Contrast injection can be helpful to detect a defect that may be otherwise difficult to identify. In isolated defects, spectral Doppler interrogation shows systolic left-to-right shunting across the ventricular septum, with a peak jet velocity inversely proportional to defect size. Turbulent color Doppler flow characterizes a small restrictive VSD, with a high peak velocity consistent with a ventricular gradient. A large, unrestrictive VSD equalizes pressures between the ventricles and elevates PASP. A significant left-to-right shunt causes left-sided volume overload, dilatating the LA and LV. *Eisenmenger syndrome*, rarely seen today, results from unrestricted interventricular shunting that alters the pulmonary vasculature and thereby increases arteriolar resistance and reverses the shunt direction from left-to-right to right-to-left. The peak velocities of the TR or VSD jets can provide an estimate of RVSP (or PASP).

The *preoperative TEE* examination should, in all cases, confirm the location, size, and number of defects; assess the chamber and PA sizes; and evaluate ventricular function [196]. Spectral Doppler interrogation can determine shunt direction and magnitude and the degree of pressure restriction and provide an estimate of PA pressures. The examination should also assess for associated cardiac anomalies, valvular competence, and outflow tract obstruction. The *post-CPB TEE* study focuses on evaluating residual shunting, PASP, and ventricular function [197]. One should note that a large proportion of residual VSD shunts are trivial and resolve spontaneously [198]. The type of VSD suggests the need for further evaluation for associated pathology, such as outflow tract obstruction, valvular regurgitation, and the adequacy of the intervention for concomitant lesions. TEE is also helpful for monitoring, guiding, and documenting the appropriate position of transcatheter muscular VSD occluder devices in the cardiac catheterization laboratory and during periventricular interventions (Figure 15.16). In fact, a recent report describes the exclusive use of TEE without fluoroscopy during transcatheter occlusion procedures [200].

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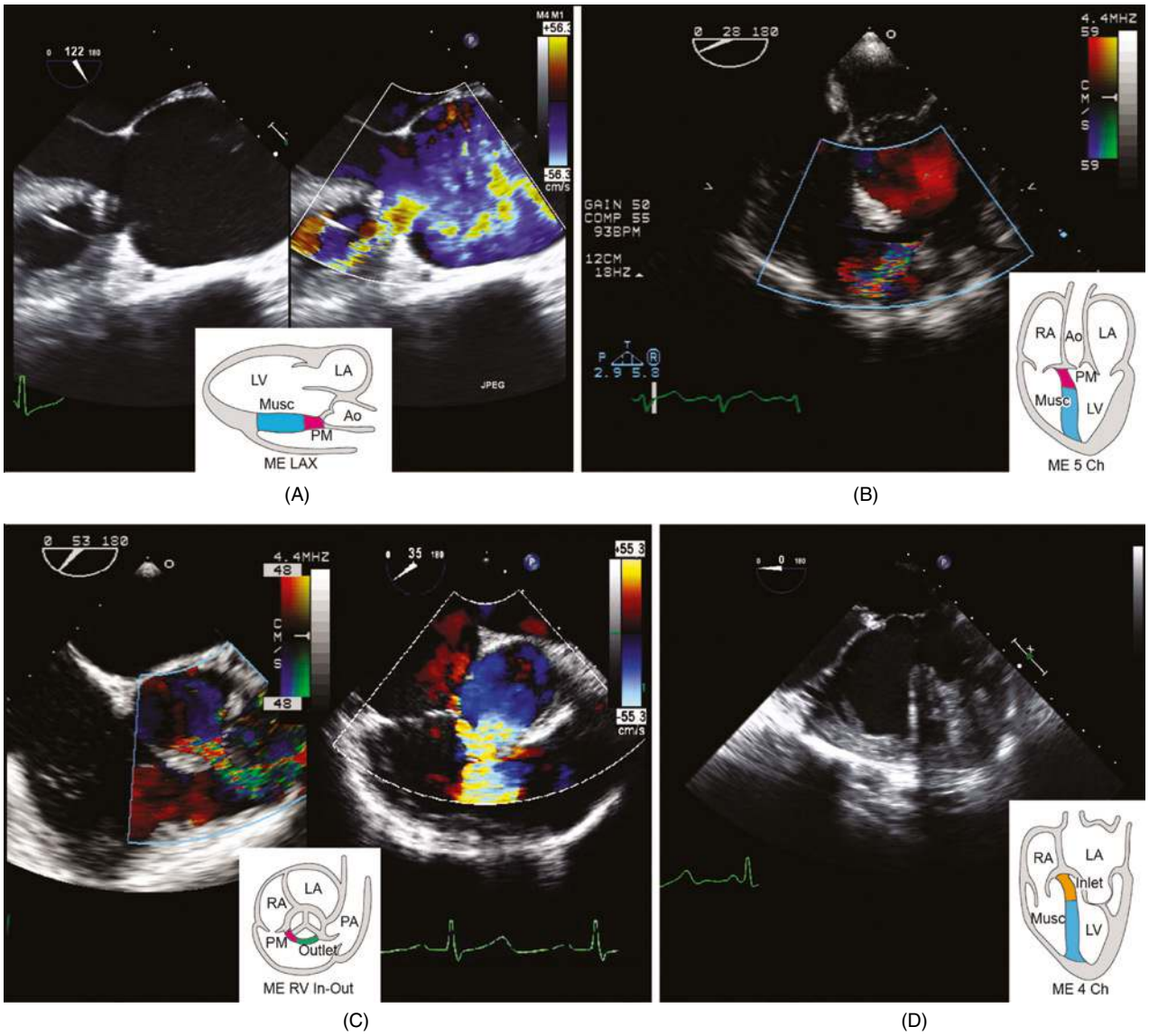


Figure 15.15 *Ventricular septal defects (VSDs)*. (A) *Perimembranous* (*PM*) *VSD*. The defect appears in cross sections that display the tricuspid valve (TV) and/or aortic valve (AoV) at the level of the midesophagus, such as ME 5-Ch, ME AoV LAX (shown), ME LAX, and right ME RV In-Out views. Associated TV abnormalities may be present (aneurysmal septal tissue partially occluding the VSD), AoV cusp prolapse, or subaortic stenosis requiring additional views for evaluation. (B) *Muscular* (*Musc*) *VSD*. The examination for this defect uses sweeps of the entire ventricular septum to identify deficiencies surrounded exclusively by muscle rims. The ME 4-Ch (shown), ME LAX, and the TG/DTG views best display this communication. Color Doppler may be necessary to demonstrate small serpiginous or, on occasion, multiple adjacent muscular defects ("Swiss cheese septum"). (C) *Outlet VSD*. The ME RV In-Out view is particularly helpful in determining the type of VSD, as a septal deficiency close to the pulmonary valve indicates an outlet VSD (*left panel*), in contrast to a PM defect located near the TV valve (*right panel*). An outlet VSD may potentially result in AoV cusp prolapse (usually of the right coronary cusp) with associated regurgitation. This is optimally examined in the ME AoV LAX view by 2D imaging and color-flow mapping. (Source: Vegas [112]. Reproduced with permission of Springer.) (D) *Inlet VSD*. The identification of this defect in the superior aspect of the muscular septum is optimal in a ME 4-Ch view that shows the region where the atrioventricular valves would normally join the interventricular septum (crux of the heart) as shown. Inlet defects are located more superiorly in the muscular septum than posterior muscular VSDs. *Ao* aorta; *LA* left atrium; *LV* left ventricle; *PA* pulmonary artery; *RA* right atrium. (Source: Diagrams courtesy of Ms. Willa Bradshaw.)

Atrioventricular septal defects

Anatomic and physiologic features

The characteristics of AVSDs, also referred to as *common AV canal* or *endocardial cushion* defects, relate to deficiencies of the AV septum and abnormalities of the AV valves. Although a well-known classification scheme recognizes only two categories of AVSDs, i.e., the complete and partial forms [201], the description of additional forms may lead to confusing nomenclature [202]. The various categories are as follows:

- *Complete defect*, characterized by a single valve annulus, common AV valve with usually five leaflets, and contiguous communications at the atrial (primum ASD) and ventricular (inlet VSD) levels

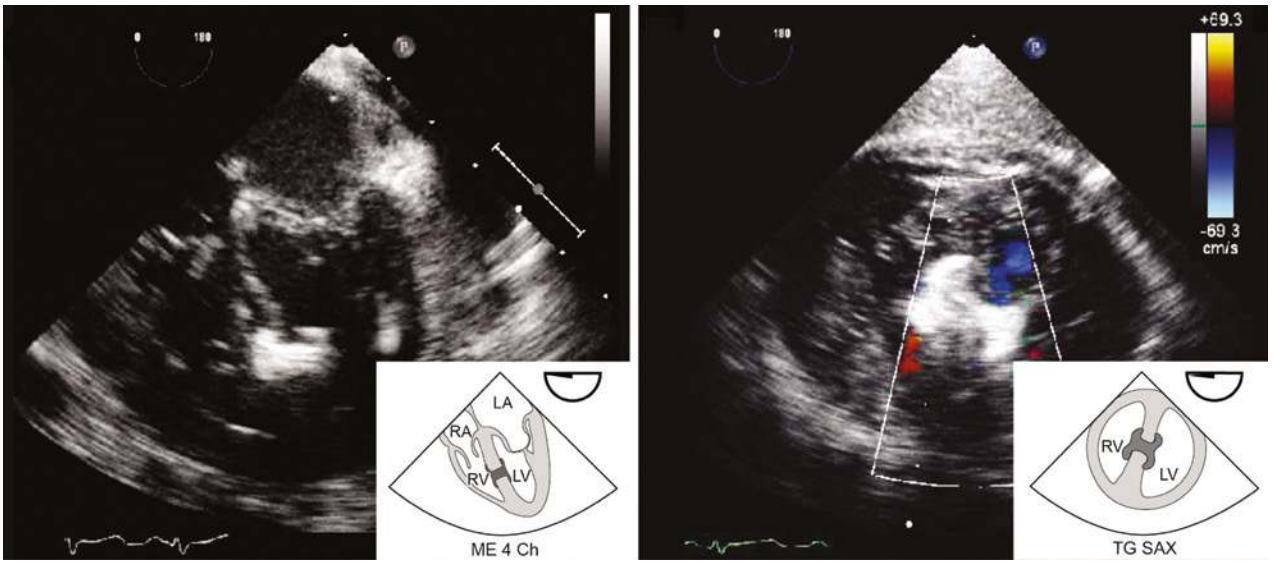


Figure 15.16 *Device occlusion of muscular ventricular septal defect (VSD).* (A) ME 4-Ch image depicts the appearance of a muscular VSD occluder device in the mid septum. (B) TG Mid Pap SAX complementary image demonstrates the position of the occluder device. *LA* left atrium; *LV* left ventricle; *RA* right atrium; *RV* right ventricle. (Source Motta and Miller-Hance [199]. Reproduced with permission of Wolters Kluwer Health, Inc.). Diagrams courtesy of Ms. Willa Bradshaw.

- *Intermediate defect*, described as having a primum ASD, large nonrestrictive VSD, and common AV valve annulus separated by a "tongue" of tissue into two valvular orifices
- *Partial defect*, consisting of a primum ASD and cleft in the left AV valve (MV). An alternative term for the cleft is the "zone of apposition."
- *Transitional defect*, having in addition to a primum ASD a small inlet VSD due mostly to obliteration by right-sided or TV valve chordal attachments to the ventricular septum

Complete defects are usually associated with significant intracardiac shunting, resulting in pulmonary overcirculation and left-sided volume overload. Intermediate defects physiologically resemble the complete form of the defect. Partial and transitional defects essentially behave as an ASD. Associated defects in the patient with an AVSD may include tetralogy of Fallot (TOF), double-outlet RV (DORV), and total anomalous pulmonary venous drainage or pulmonary atresia in more complex, heterotaxy-type defects.

Highlights of the TEE examination

The ME 4-Ch view best shows these types of defects (Figure 15.17). The comprehensive *pre-CPB TEE* assessment of these anomalies uses multiple planes of interrogation and a combination of all Doppler modalities for a detailed evaluation [203, 204]. Initial experience has shown real-time 3D TEE to be extremely helpful in revealing the anatomic features of AVSDs [92]. The *post-CPB TEE* examination should evaluate for residual intracardiac shunts, AV valve dysfunction (regurgitation or stenosis), subaortic obstruction, PASP elevation, and ventricular function.

LV outflow obstruction

Anatomic and physiologic features

Obstruction along the LV outflow tract (LVOT) can occur at the subvalvular, valvular, or supravalvular levels, or it can be more distally situated (as in CoA or aortic arch interruption). *Subvalvular aortic stenosis* arises from a discrete membrane, fibromuscular ring, or muscular tunnel obstruction, with associated lesions such as CoA and MV abnormalities. Shone complex consists of a subaortic membrane, bicuspid AoV (BAV), supravalvular mitral ring, and CoA. *Valvular aortic stenosis* can arise in association with a BAV from valve thickening or progressive calcification. Coexisting lesions can include PDA, CoA, and other left-sided obstructive pathology. BAV is associated with the potential for valvular regurgitation or aortic root dilatation from an ascending aortopathy. *Supravalvular aortic stenosis* involves narrowing of the ascending Ao at the sinotubular junction, a pathology most commonly afflicting children with Williams syndrome. An obstructive arteriopathy can affect various regions of the Ao, aortic arch vessels, and even the coronary arteries in some cases. The physiological repercussions of any form of LVOT obstruction relate to impedance of LV ejection, resulting in elevation of systolic pressure, a gradient between the proximal and distal regions across the obstruction, increased myocardial force, and LV wall stress.

Highlights of the TEE examination

2D and real-time 3D TEE can adequately characterize anatomy and identify pathology in the outflow tract, AoV, and aortic root [205–209]. Alternate imaging modalities such as CMR or CT may be needed to define the anatomy of the Ao

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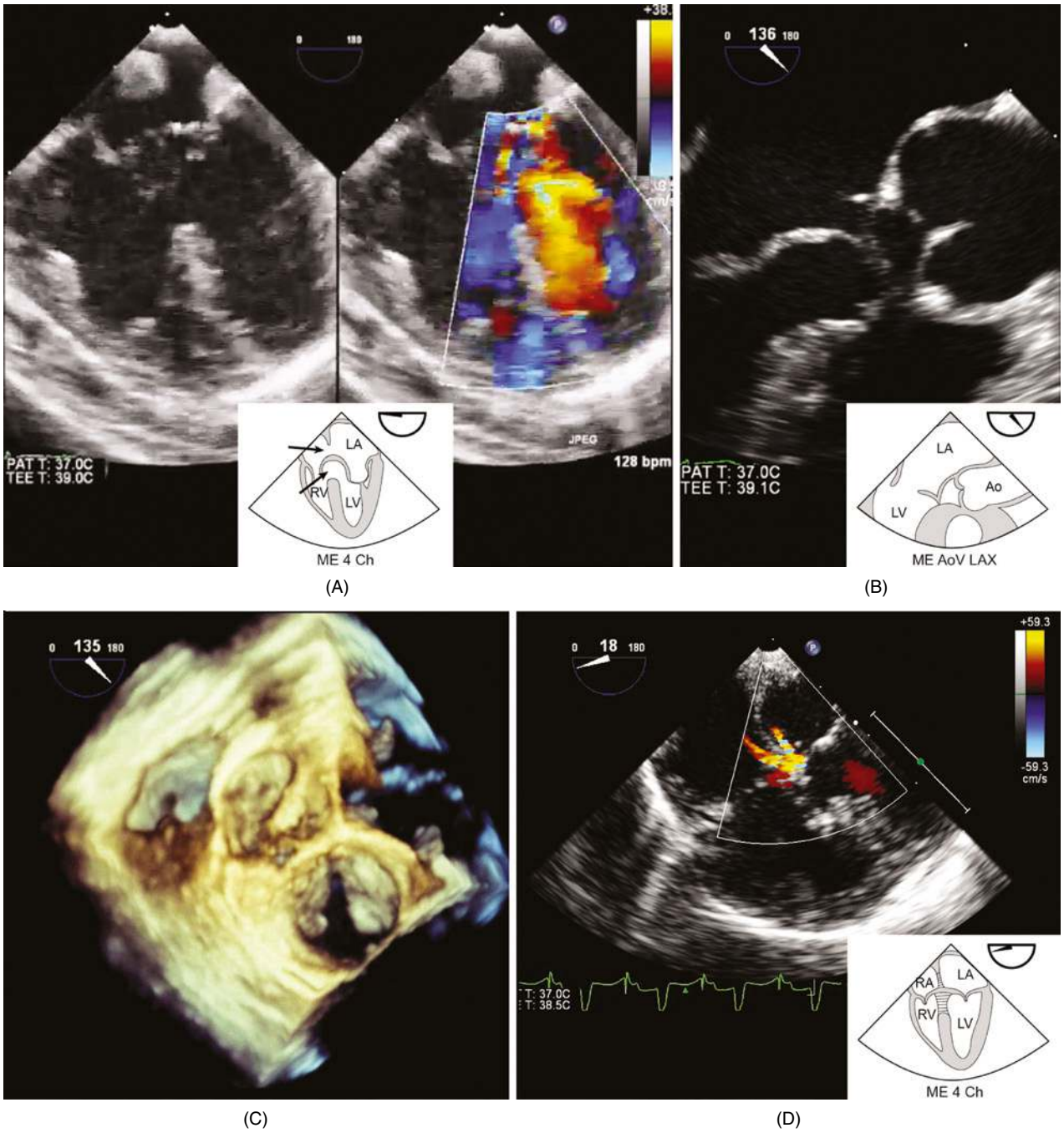


Figure 15.17 *Atrioventricular septal defect (AVSD)*. (A) *Septal defects*. ME 4-Ch views depict a primum atrial septal defect and an inlet ventricular septal defect in an AVSD (*arrows*). Additional aspects of the evaluation should include determination of shunt flow by color Doppler, morphology and function of valvular structures, and ventricular size and function. (B) *Subaortic stenosis*. Left ventricular (*LV*) outflow tract obstruction may be caused by atrioventricular valve (AVV) attachments to the interventricular septum or elongation of the outflow related to LV inlet–outlet disproportion. This is best displayed in the ME 5-Ch, ME LAX (shown), TG LAX, and DTG 5-Ch views. (C) *Left AVV cleft*. An *en face* view clearly displays a cleft in the left AVV by 3D TEE imaging. Superimposed color Doppler permits characterization of associated regurgitant jets. (D) *Post–cardiopulmonary bypass examination*. The postrepair evaluation focuses on the assessment of AVV function to exclude significant regurgitation or stenosis and the presence of residual intracardiac shunts. A ME 4-Ch image depicts a tiny LV to right atrial (*RA*) shunt and a trivial amount of regurgitation at the septal aspect of the left AVV (base of the cleft). *Ao* aorta; *LA* left atrium; *RV* right ventricle. Diagrams courtesy of Ms. Willa Bradshaw.

and its branches more precisely in selected cases. Regardless of the specific cause of the obstruction, the TEE examination should include assessment of AoV morphology and function, aortic annulus and root size, and the LV to determine its size, wall thickness, and function (Figure 15.18). Depending on the type of obstructive pathology, details of relevance in the TEE examination include the presence and severity of associated aortic annular or root hypoplasia, aortic root dilation (poststenotic or otherwise), and other coexisting lesions. Cross sections in the mid- and upper esophagus facilitate the examination of the mid-ascending Ao (ME Asc Ao LAX) and aortic arch (UE Ao Arch LAX and SAX views). Transgastric (TG LAX) and DTG (DTG 5-Ch) imaging is extremely useful in assessing outflow tract gradients as these windows allow Doppler interrogation parallel to the direction of flow.

The interventions for LVOT pathology involve a variety of approaches that aim to alleviate the obstruction. The specific intervention, operation, or catheter-based procedure dictates how the TEE examination is performed, but it often consists of determining the residual severity of any outflow obstruction and evaluating AoV competency [161]. After a subaortic resection, it is important to exclude the presence of an iatrogenic VSD or damage to the MV. In the case of autologous PV replacement of a diseased AoV (Ross procedure), relevant aspects of the examination include assessing graft function (autograft and PV allograft) and analyzing segmental wall motion to identify complications related to coronary reimplantation. A similar approach is warranted for Ao root replacement. Evaluating prosthetic valve function and excluding paravalvular leakage are essential after AoV replacement.

RV outflow obstruction

Anatomic and physiologic features

As in the case of LVOT obstructive lesions, those that affect the RV outflow tract (RVOT) may be isolated to the subvalvular, valvular, or supravalvular levels, or they may concomitantly involve multiple regions. Pulmonary (or pulmonic) valve stenosis (PS) is the most common lesion and is characterized by leaflet thickening or fusion resulting in valvular narrowing. The variable size of the valvular orifice accounts for the severity of the obstruction. Less frequently, valvular dysplasia causes the stenosis. Associated defects include ASD, VSD, and obstructive subpulmonary hypertrophy.

Obstruction of the RVOT results in an elevated RVSP and wall hypertrophy, usually proportional to the degree of obstruction. Severe pressure loads can, in some cases, result in RV dilation and failure.

Highlights of the TEE examination

The best views for examining the malformation that causes severe valvular PS include the ME RV In-Out, ME PA, ME Asc Ao SAX, and UE Ao Arch SAX views (Figure 15.19). Typical findings include valvular doming and reduced systolic leaflet excursion. Color Doppler shows turbulent antegrade flow at the level of the valve and, depending on associated pathology, in adjacent subvalvular or supravalvular regions [210]. Pulmonary regurgitation can also be present. Pulsed-wave Doppler can establish the level, and continuous-wave Doppler can determine the pressure gradient across the obstruction. As in the case of LVOT obstruction, TG and DTG views may permit better Doppler alignment, particularly if the UE views are unobtainable. Estimating RVSP from the peak velocity of the TR jet provides another parameter to determine the severity of the obstruction. Severe PS causes RV hypertrophy, as detected in the ME 4-Ch and ME RV In-Out views and in cross sections that display the RV in the TG and DTG windows. Systolic interventricular septal flattening appears in most cases of severe valve obstruction with preserved RV function. Poststenotic dilatation of the main PA may be present.

In most cases, catheter interventions can manage isolated valvular PS. Real-time 3D TEE can enhance monitoring during percutaneous valvuloplasty in anesthetized patients [211]. In those undergoing surgery for pathology that affects the valve itself, adjacent regions, or multiple levels, after the obstruction is relieved, the *post-CPB TEE* examines the residual outflow PG, determines the severity of any pulmonary regurgitation, identifies new pathology (VSD, TR), and assesses biventricular function. The need to address associated lesions guides any additional applications of TEE.

Tetralogy of Fallot

Anatomic and physiologic features

In the classic lesion, the four components of TOF consist of a large VSD, RVOT obstruction, aortic override, and RV hypertrophy. The diverse clinical manifestations in this lesion relate to its variable anatomic features, particularly the severity of the RVOT obstruction. Associated findings may include an atrial-level communication (PFO or ASD), additional VSDs, an LSVC-to-coronary sinus connection, coronary artery anomalies, and variants of aortic arch sidedness or branching pattern. Concomitant lesions such as an AVSD (colloquially referred to as "tet-canal" defect) are found in some cases. Pulmonary atresia with a VSD represents a severe form of disease in TOF.

Highlights of the TEE examination

The abnormalities that comprise the TOF spectrum are easily identifiable by TEE (Figure 15.20) [199]. The TEE examination requires detailed interrogation of the RVOT and the main and proximal branch PAs from the UE, ME, and DTG levels. Spectral and color Doppler are essential for determining the level and severity of the obstruction. Examining the ventricular septum requires multiple views that display the VSD and excludes additional communications at the ventricular level as described in the prior section on VSDs. The ME 4-Ch, TG, and DTG views can assess RV size, chamber hypertrophy, and function. Additional TEE planes of interrogation are necessary to assess associated defects.

Postoperative TEE after complete repair of TOF evaluates for residual RVOT obstruction, PV competence, VSD patch leak, and ventricular function [79, 212–214]. Patients who have undergone TOF repair in infancy or childhood present most often in late adolescence or adulthood with pulmonary regurgitation and the effects of chronic volume overload to the right heart. In some cases, the RV and even the LV have detectable systolic impairment. Residual RVOT obstruction and intracardiac shunts should be explored by using similar TEE views to those used to evaluate the uncorrected lesion.

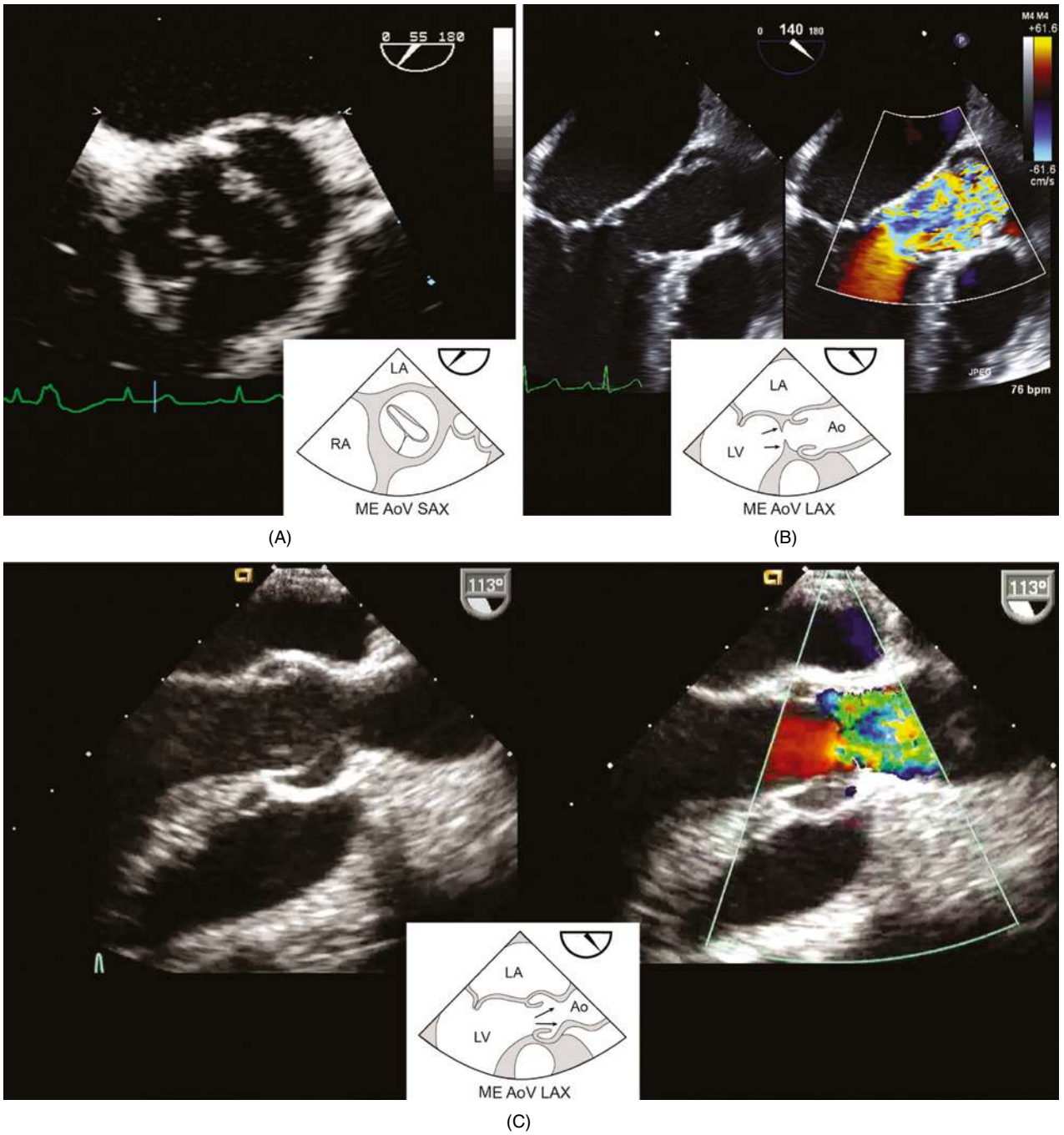


Figure 15.18 *Left ventricular outflow tract (LVOT) obstruction*. (A) *Valvular aortic stenosis*. In aortic valve (AoV) stenosis, the number and mobility of the leaflets and the qualitative severity of the obstruction are best appreciated in the ME AoV SAX and ME AoV LAX views. The ME AoV SAX image shows a systolic frame of a functionally bicuspid AoV; note the presence of commissural fusion. (B) *Subaortic stenosis*. 2D and color Doppler interrogation of a fibromuscular membrane (*arrows*) causing subaortic stenosis in the ME AoV LAX view. This cross section, in addition to the ME 5-Ch, TG LAX, and DTG 5-Ch views, is essential in defining the level and nature of the obstruction in any of the lesions that affect the LVOT. Superimposed color-flow Doppler demonstrates turbulence at the level of the obstruction (as shown) and permits evaluation of AoV function. Continuous-wave Doppler interrogation in the TG and DTG views can determine the pressure gradient across the region, whereas pulsed-wave Doppler defines the level of obstruction. Abnormal AoV systolic closure and/or fluttering of the valvular cusps, if present, are best shown in the ME AoV SAX and LAX views. (Source: Vegas et al. [41]. Reproduced with permission of Springer Nature.) (C) *Supravalvular aortic stenosis*. The typical hourglass deformity (*arrows*) at the Ao sinotubular junction appears in the ME AoV LAX view (as shown) by 2D imaging and color-flow Doppler (note the site of color aliasing). Dilation of the coronary arteries may result from exposure to high left ventricular (*LV*) pressures (best seen in the ME AoV SAX and ME AoV LAX views with multiplane angle adjustments). The potential for myocardial ischemia from compromised coronary blood flow in this lesion can manifest on TEE as segmental wall motion abnormalities and requires a combination of views that display the various regions of the myocardium (refer to Figure 15.11). *Ao* aorta; *LA* left atrium; *RA* right atrium. Diagrams courtesy of Ms. Willa Bradshaw.

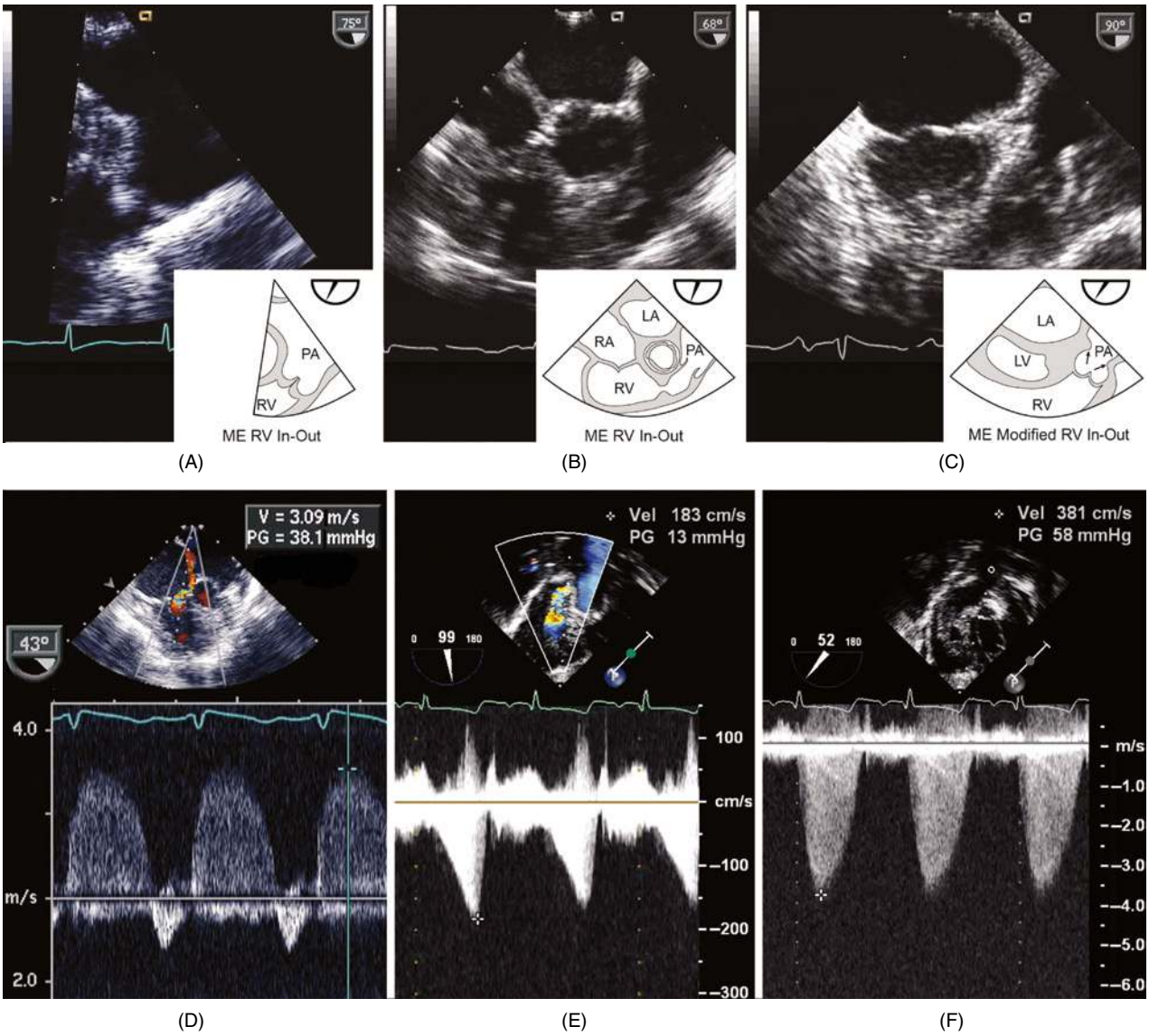


Figure 15.19 *Right ventricular outflow tract (RVOT) obstruction*. (A) *Valvular pulmonary stenosis (PS)*. Stenosis of the pulmonary valve (PV) can be due to valvular thickening, commissural fusion, and/or valvular dysplasia. The malformation is best examined in the ME RV In-Out, UE PA, ME Asc Ao SAX, and UE Ao Arch SAX views. Typical findings include valvular doming and reduced systolic leaflet excursion. The zoomed view shown in a ME In-Out view depicts a thickened PV and associated poststenotic dilation of the main pulmonary artery (*PA*) in a patient with valvular stenosis. (B) *Subvalvular PS*. Muscular hypertrophy of the subvalvular pulmonary region can occur in isolation or may be present in association with valvular PS. The narrowing of this region of the right ventricle (*RV*) can be fixed or dynamic in nature. The ME RV In-Out image displays severe subvalvular narrowing. (C) *Supravalvular PS*. Discreet narrowing of the supravalvular region occasionally occurs in association with valvular PS or the pathology can be found in isolation. This is best examined in views that display the pulmonary outflow tract in its long axis, as shown in a modified ME RV In-Out view (*arrows*). (D) *Estimation of right ventricular systolic pressure* (*RVSP*). Moderate-to-severe RVOT obstruction is frequently associated with some degree of tricuspid regurgitation (TR). The peak velocity of the TR jet, as shown, allows estimation of the RVSP, providing another parameter to assess the severity of the outflow obstruction. In this example, the RVSP, as derived from the simplified Bernoulli equation, is ~48 mmHg calculated as follows: [(3.09)^2 + right atrial (*RA*) pressure (assumed ~10 mmHg)]. The RVSP in this case does not reflect the pulmonary artery systolic pressure. (E) *Spectral Doppler*. Interrogation using spectral Doppler from the DTG RVOT view depicts the late systolic, "dagger-shaped" signal, that characterizes dynamic obstruction. (F) *Continuous-wave* (*CW*) *Doppler*. The image depicts the optimal cursor alignment for spectral Doppler interrogation that can be obtained from DTG imaging. In this example, CW Doppler measures the peak systolic pressure gradient between the RV and the PA (58 mmHg) and is able to estimate the severity of the RVOT obstruction. *LA* left atrium; *LV* left ventricle. Diagrams courtesy of Ms. Willa Bradshaw.

Double-outlet right ventricle

Anatomic and physiologic features

A DORV refers to a VA connection in which there is near or complete alignment of both great arteries to the RV. The exact diagnostic criteria for DORV are controversial. It does not represent a single disease but rather a spectrum of pathologies that may share features with other lesions such as TOF and transposition [215]. A VSD is almost always present. The location of the VSD and its relation to the great vessels play a critical role in the physiology and can be subaortic (most

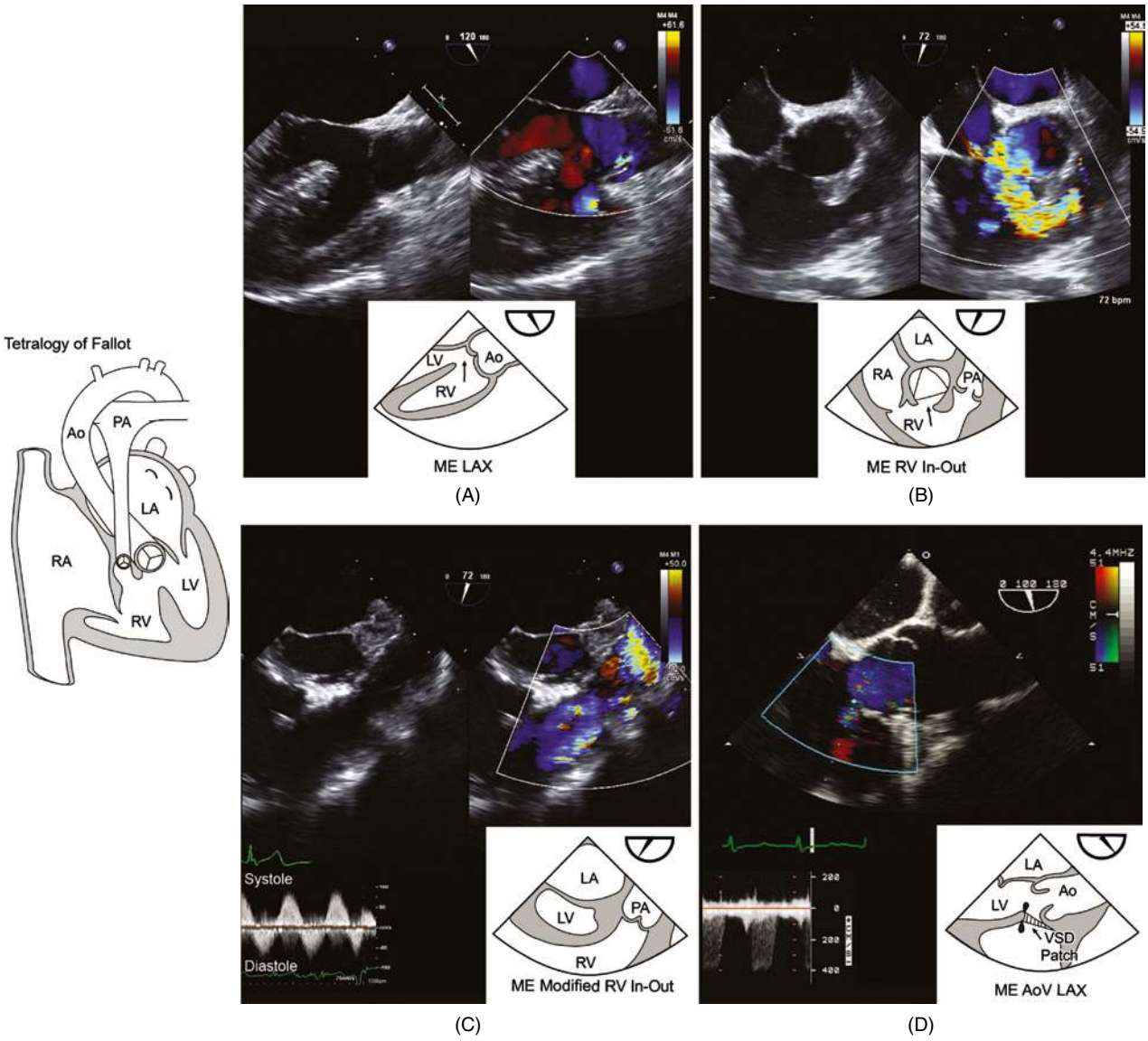


Figure 15.20 *Tetralogy of Fallot (TOF)*. (A) *Conoventricular ventricular septal defect* (*VSD*). The large VSD in TOF (*arrow*) is optimally displayed in the ME LAX (shown), ME 5-Ch, ME RV In-Out; panel B), and DTG views. These same views display the aortic (*Ao*) override over the VSD. Color Doppler facilitates assessment of defect size and direction of shunting. (B) *Right ventricular outflow tract* (*RVOT*) *obstruction*. The RVOT (subvalvular, valvular, and supravalvular areas) is best evaluated in the ME RV In-Out view. The typical anterior and leftward deviation of the conal or infundibular septum that causes subpulmonary muscular dynamic obstruction, as well as the VSD (*arrow*), can be optimally displayed in this view as shown. (C) *Pulmonary regurgitation*. Transannular patch repair in TOF resulting in pulmonary regurgitation is best evaluated in views that display the RVOT in long axis as shown. Note the blue color Doppler jet representing flow into the right ventricle (*RV*) during diastole and the to-and-fro flow across the RVOT by spectral Doppler. (D) *VSD patch leak*. Assessment of residual ventricular level shunting is an important component of the postrepair TEE examination after corrective surgery and during subsequent reoperations in TOF. The ME AoV LAX view shown depicts a VSD patch (*arrow*) with a small leak by color Doppler and associated high-velocity left-to-right shunting by spectral Doppler. *LA* left atrium; *LV* left ventricle; *PA* pulmonary artery; *RA* right atrium. Diagrams courtesy of Ms. Willa Bradshaw.

commonly), subpulmonary (i.e., Taussig-Bing anomaly), doubly committed, or noncommitted (remote). The spatial orientation of the great vessels is frequently abnormal and can be side by side or in the configuration of D-transposition of the great arteries (D-TGA). The physiologic manifestations are variable and can mimic those of an isolated VSD, TOF, D-TGA, or single ventricle. Lesion heterogeneity necessitates careful preoperative assessment and surgical planning.

Highlights of the TEE examination

Preoperative TEE evaluates the location and size of the VSD and its relationship to the great arteries (Figure 15.21). The spectral and color Doppler modalities are important in assessing flow out of the LV and across the VSD when the defect is subaortic in location. These modalities are essential in evaluating the severity of associated outflow tract obstruction (right and left) and valvular function (stenosis or regurgitation).

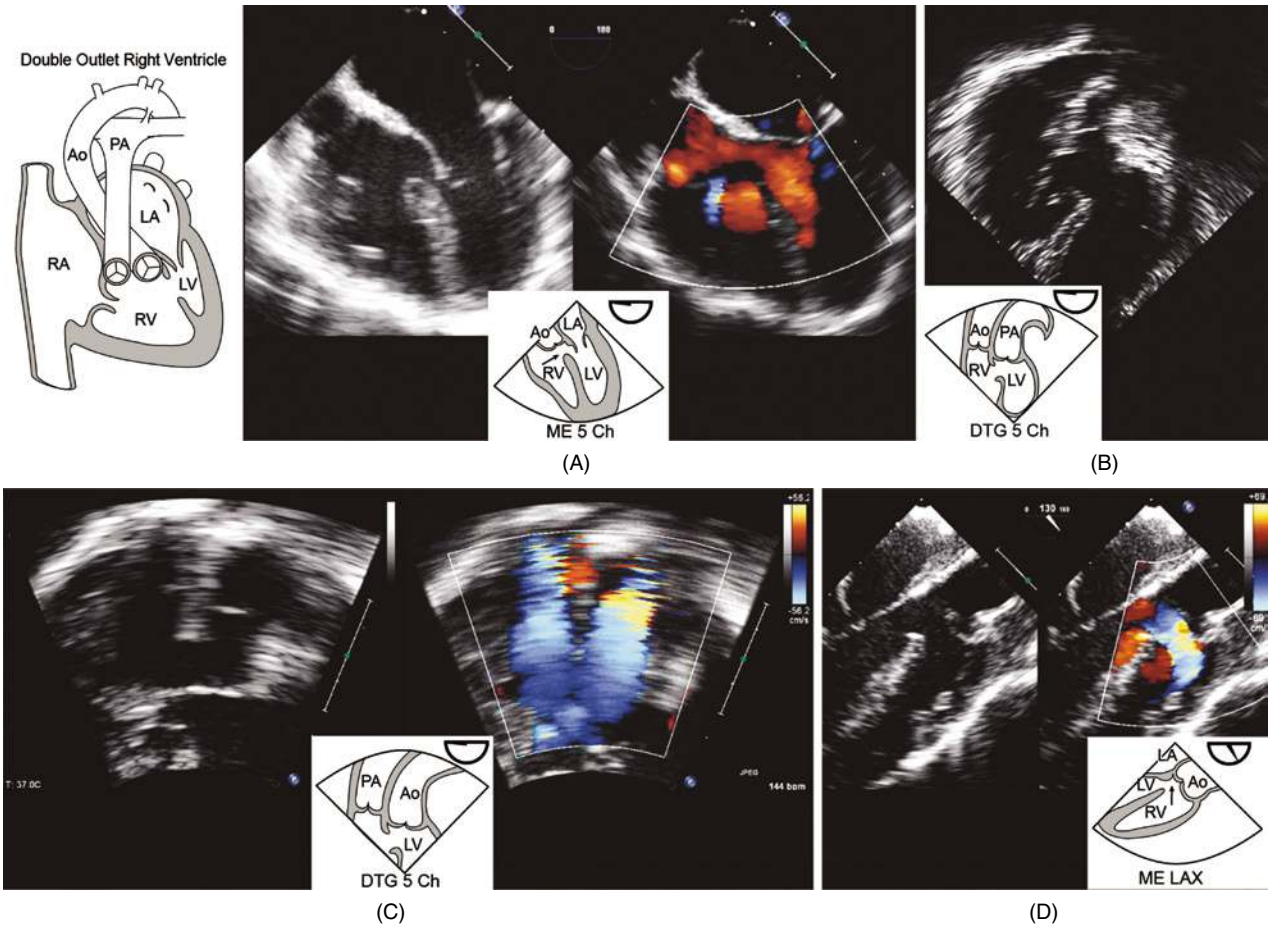


Figure 15.21 *Double-outlet right ventricle (DORV)*. (A) *Subaortic ventricular septal defect (VSD)*. *Left panel*: ME 5-Ch view depicting the most common variant of DORV with a malalignment VSD in subaortic location. Note the ventricular communication (*arrow*), the abnormal relationship of the aorta (*Ao*) over the right ventricle (*RV*), and the presence of a muscular conus resulting in mitro-aortic discontinuity. Color and spectral Doppler in the ME views (4-Ch, 5-Ch, LAX) outline the direction and pattern of shunting across the VSD. R*ight panel*: the unusual long pathway of blood flow from the left ventricle (*LV*) to the Ao, as shown by color Doppler, represents a substrate for potential subaortic stenosis after the repair. (B) *Subpulmonary VSD*. DTG 5-Ch view in the Taussig-Bing anomaly depicting the relationship of the great arteries in this defect and the subpulmonary location of the VSD accounting for preferential flow of LV blood into the pulmonary artery (*PA*) and the physiology of D-transposition of the great arteries. (C) *Side-by-side great arteries*. The abnormal side-by-side spatial orientation of the great arteries in DORV (patient with a subaortic VSD) is noted in these zoomed 2D and color Doppler images. This relationship contrasts with their crisscross orientation in the normal heart. (D) *VSD flow*. ME LAX view in same patient as in panel C with DORV depicting the relationship of the VSD to the Ao and evaluation of VSD flow by color-flow Doppler (*arrow*). *LA* left atrium; *RA* right atrium. Diagrams courtesy of Ms. Willa Bradshaw.

In most instances for which a biventricular repair is feasible, surgery aims to restore normal anatomy by establishing continuity between the ventricles and corresponding great arteries using various surgical techniques. In cases involving pulmonary stenosis, distinguishing this anomaly from TOF is important. Although the physiology of the two lesions is similar, a subaortic conus in the patient with TOF-like DORV represents a substrate for subaortic stenosis after the repair, a rare occurrence in TOF. All TEE views that display the pathway of the blood flow between the LV and the Ao (e.g., ME 5-Ch, ME LAX, TG LAX, and DTG 5-Ch) should explore this potential problem. In addition, *postrepair TEE*, depending on the details of the anatomy and type of the intervention, should exclude residual intracardiac shunting, evaluate for any other forms of outflow tract obstruction and valvular regurgitation, and assess ventricular function.

Transposition of the great arteries

Anatomic and physiologic features

In D-TGA, the AV connections are concordant and the VA connections are discordant. The segmental anatomy as per the Van Praagh short-hand notation in most cases is that of {S,D,D}, meaning normal visceroatrial arrangement or visceroatrial situs solitus, D-loop ventricles, and D-transposition (denoting the position and relationship of the great arteries). Whereas in the normal heart the Ao is posterior and rightward of the anterior and leftward PA, in this arrangement the Ao originates from the RV anteriorly and to the right of the posterior and leftward PA. Separate parallel circulations characterize the physiology. A communication, usually an ASD or a PDA, is essential for intercirculatory mixing and to allow partially oxygenated blood to reach the systemic circulation. In most cases, the ventricular septum is intact, but VSDs of various sizes can be present. Associated

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findings can include pulmonary outflow obstruction, coronary artery variants, and aortic arch anomalies.

Highlights of the TEE examination

The TEE evaluation in the patient with D-TGA requires proper 2D identification of cardiac chambers and connections (Figure 15.22). Additional indispensable TEE information includes confirming the segmental venoatrial connections (ME Bicaval, TG IVC/Hep veins); evaluating the AV valves, ventricular septum, and ventricular function (ME views: 4-Ch, 2-Ch, 5-Ch, LAX; TG views: Basal SAX, Mid Pap SAX, Apical SAX); assessing the LVOT and PV (ME views: LAX, 5-Ch, AoV SAX, and AoV LAX; TG LAX; DTG 5-Ch); examining the RVOT and AoV (ME RV In-Out and DTG RVOT views); and interrogating the IAS (ME 4-Ch, ME Bicaval, and DTG Atr Sept). In addition to the 2D evaluation, the examination should include interrogation of the outflow tracts for obstruction, the semilunar valves for stenosis or regurgitation, and the origin of the coronary arteries. A comprehensive assessment of the aortic arch may not be feasible with TEE, but a combination of views at the UE and ME levels may offer limited interrogation. If necessary, epicardial imaging can provide additional views.

Surgical correction of D-TGA aims to restore the proper sequence of blood flow. The favored surgical approach is the *arterial switch operation* (ASO), an anatomic correction that restores the normal VA relationships. It involves transecting and anastomosing the great arteries to their respective appropriate ventricles and translocating the coronary arteries. TEE can reveal immediate complications after the ASO, including anastomotic site stenosis causing supravalvular obstruction in the PA or Ao [216]; ASD or VSD patch leaks, valve regurgitation, and ventricular dysfunction [216]. Coronary complications should be suspected if global systolic function is impaired or segmental wall motion abnormalities are present [124, 125]. Both TEE and E-echo have been shown to be of benefit in evaluating segmental wall motion abnormalities

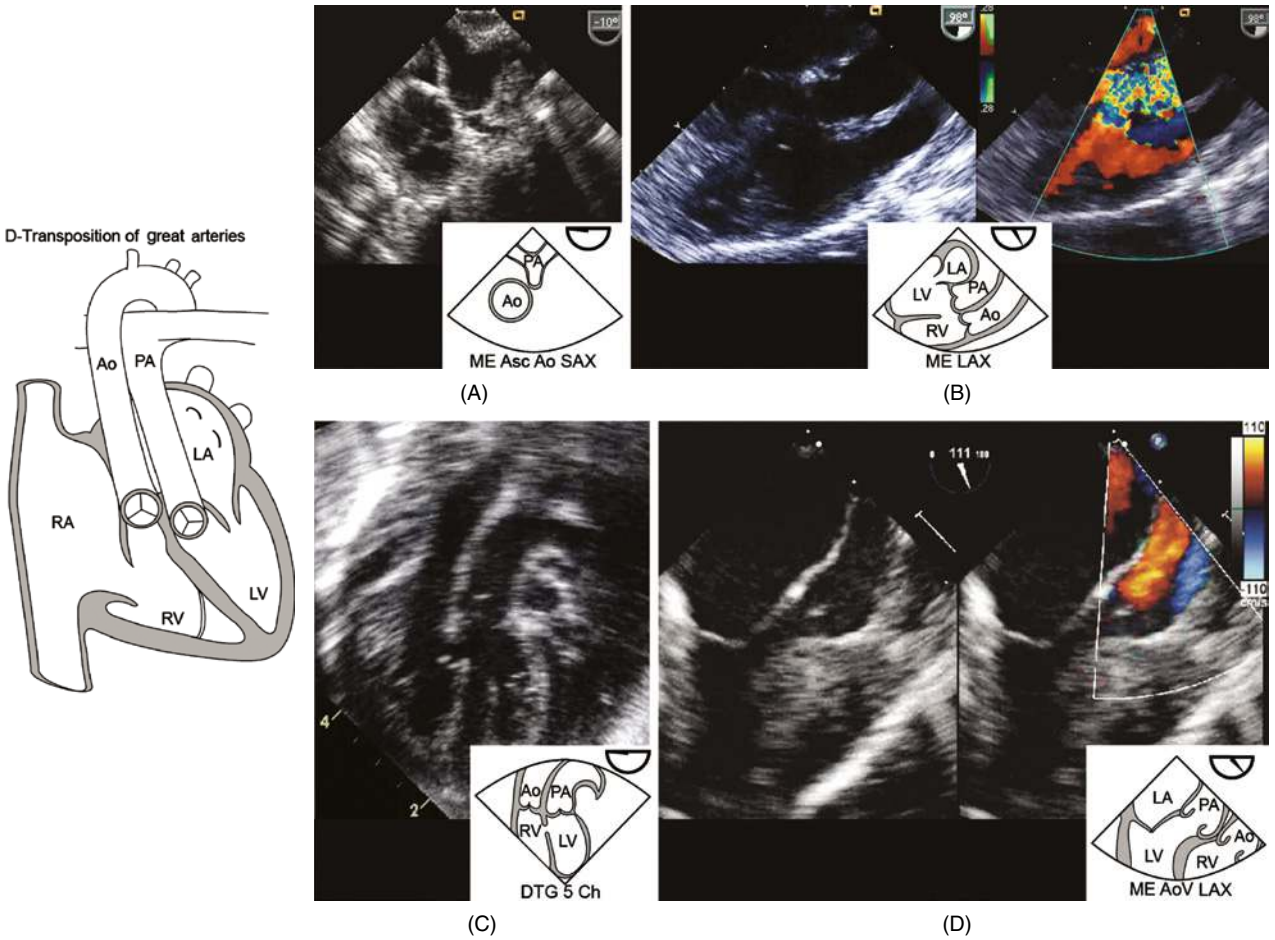


Figure 15.22 *D-Transposition of the great arteries (D-TGA).* (A) *Orientation of the great arteries*. ME Asc Ao SAX view displaying the anterior and rightward aorta (*Ao*) with respect to the posterior and leftward bifurcated pulmonary artery (*PA*) in D-TGA. (B) *Ventricular septal defect* (*VSD*). 2D and corresponding color Doppler images in the ME LAX view in an infant with D-TGA and associated VSD. Note the abnormal parallel orientation of the great arteries (in contrast to their normal crisscross relationship) and flow from the higher pressure right ventricle (*RV*) across the VSD into the left ventricle (*LV*) and PA (red flow). (C) *Ventriculoarterial* (*VA*) *connections*. DTG 5-Ch view depicting the discordant VA connections in D-TGA (Ao from the RV and PA from the LV). A perimembranous VSD is readily appreciated in this 2D image. This view permits optimal spectral Doppler alignment across the outflow tracts and great vessels for assessment of patency/obstruction. (D) *Patent ductus arteriosus (PDA)*. ME LAX 2D and color Doppler images displaying the outlet of the LV into the PA. Note the PDA flow (blue signal away from the transducer) into the PA. *LA* left atrium; *RA* right atrium. Diagrams courtesy of Ms. Willa Bradshaw.

and coronary artery patency [125, 217, 218]. Excellent agreement has been reported between TEE and E-echo coronary Doppler flow patterns, as importantly, abnormalities have been correlated with adverse myocardial events [219]. The atrial switch (Senning and Mustard operation) provides physiologic correction by using intra-atrial baffles to allow deoxygenated blood to reach the PAs and the ejection of oxygenated blood into the Ao (Figure 15.23). It is no longer the surgical intervention of choice because the morphologic RV remains as the systemic pump for life. Most patients who have undergone this procedure are adult survivors of CHD. In patients with prior *Rastelli-type operation*s, which route the LV output to the Ao across a baffle and place an RV-to-PA conduit, color and spectral Doppler can assess outflow obstruction, pulmonary or aortic regurgitation, and residual VSD and estimate PASP.

Congenitally corrected transposition of the great arteries

Anatomic and physiologic features

In congenitally corrected transposition of the great arteries (CCTGA), also referred to as physiologically corrected transposition, the AV and VA connections are both discordant (double discordance). The ventricles and great vessels are malpositioned, with inversion of the ventricles and transposition of the great arteries. Although the anatomy is variable, in most cases, it consists of levocardia and visceroatrial situs solitus, with systemic veins draining into a right-sided RA connected to a right-sided morphologic LV that ejects across a rightward and posterior PA; the pulmonary veins drain into a left-sided LA, which is connected to a left-sided morphologic RV (L-ventricular loop that ejects across a leftward and anterior Ao (L-positioned great arteries). This segmental anatomy is referred to as {S,L,L} or simply as L-TGA. In this malformation, the morphologic LV represents the venous, pulmonary ventricle, and the morphologic RV functions as the arterial, systemic ventricle. The physiology is correct as desaturated blood reaches the pulmonary circulation and saturated blood enters the systemic circulation. Associated anomalies can include a VSD, pulmonary stenosis or obstruction to morphologic LV outflow, and abnormalities of the TV (Ebstein-like anomaly and others). The patient with CCTGA may present late in adulthood with TR and systemic RV failure or complete heart block.

Highlights of the TEE examination

Diagnosis of CCTGA relies on the accurate identification of cardiac chamber morphology (Figure 15.24). In addition to confirming the anatomy, an important role of TEE in this defect is assessing TV competence (systemic or left-sided AV valve), evaluation of associated defects, and determination of the functional status of the RV.

Depending on the type of surgical intervention for this lesion (e.g., conduits, baffles, and switches), TEE assists in the *post-CPB* assessment by excluding hemodynamically significant residual lesions that may necessitate revision and evaluating AV and semilunar valve competence, outflow tract obstruction, and ventricular function.

Truncus arteriosus

Anatomic and physiologic features

Truncus arteriosus refers to the anomaly that has a single arterial trunk from which both the PA and the Ao (with coronary arteries) originate. Both ventricles have a single, common outlet, and the truncal root overrides a VSD. Hypoxemia results from complete admixture of deoxygenated and oxygenated blood. Various classification schemes describe this lesion. Classification of this defect into three types (i.e., I, II, and III) in the Collet and Edwards scheme is based on the origin of the PAs from the truncal root. The clinical manifestations of this lesion depend largely on the status of the pulmonary vascular resistance and the presence of any intrinsic stenosis in the PAs. Associated findings can include truncal valve anomalies, right aortic arch, interrupted aortic arch, and coronary ostial anomalies.

Highlights of the TEE examination

The common arterial trunk has a single semilunar valve that can have variable cusp number and morphology and can be stenotic or regurgitant (Figure 15.25). A comprehensive *pre-CPB TEE* examination includes assessing truncal valve function and other coexistent lesions.

Corrective surgery for this lesion involves closing the VSD, detaching the main PA segment or individual branches from the truncal root and repairing the wall defect, and establishing continuity between the RV and the PA, usually by placing a conduit. Interventions on the truncal valve may be necessary during the initial operation or subsequently. *Post-CPB TEE* excludes residual VSD shunting and assesses the function of the truncal valve, the RV-to-PA conduit, and both ventricles. Coronary artery perfusion may be compromised preoperatively and postoperatively, resulting in global or regional wall motion abnormalities. The RV may dilate and underperform in the face of increased PASP as assessed from estimates of RVSP. In the long term, issues associated with conduit stenosis or regurgitation or truncal valve problems may lead to reoperation. The role of TEE in this scenario, in addition to assessing the specifics of the intervention, is similar to its role immediately after the initial corrective procedure.

Single ventricle

Anatomic and physiologic features

The single ventricle (univentricular heart) spectrum comprises lesions with an atretic AV valve (MV or TV), hypoplastic ventricle (e.g., hypoplastic left heart syndrome and double-inlet LV), and others for which physiologically a biventricular repair is not feasible or desirable (e.g., functional single ventricle). Frequently, a characteristic of this broad group of lesions is complete admixture of systemic and pulmonary venous blood at the atrial or ventricular level. Another common finding is systemic or pulmonary outflow obstruction.

Highlights of the TEE examination

A complete and systematic TEE examination should be the goal in all cases. However, considering the many defects that fit into the single ventricle category, the evaluation should be

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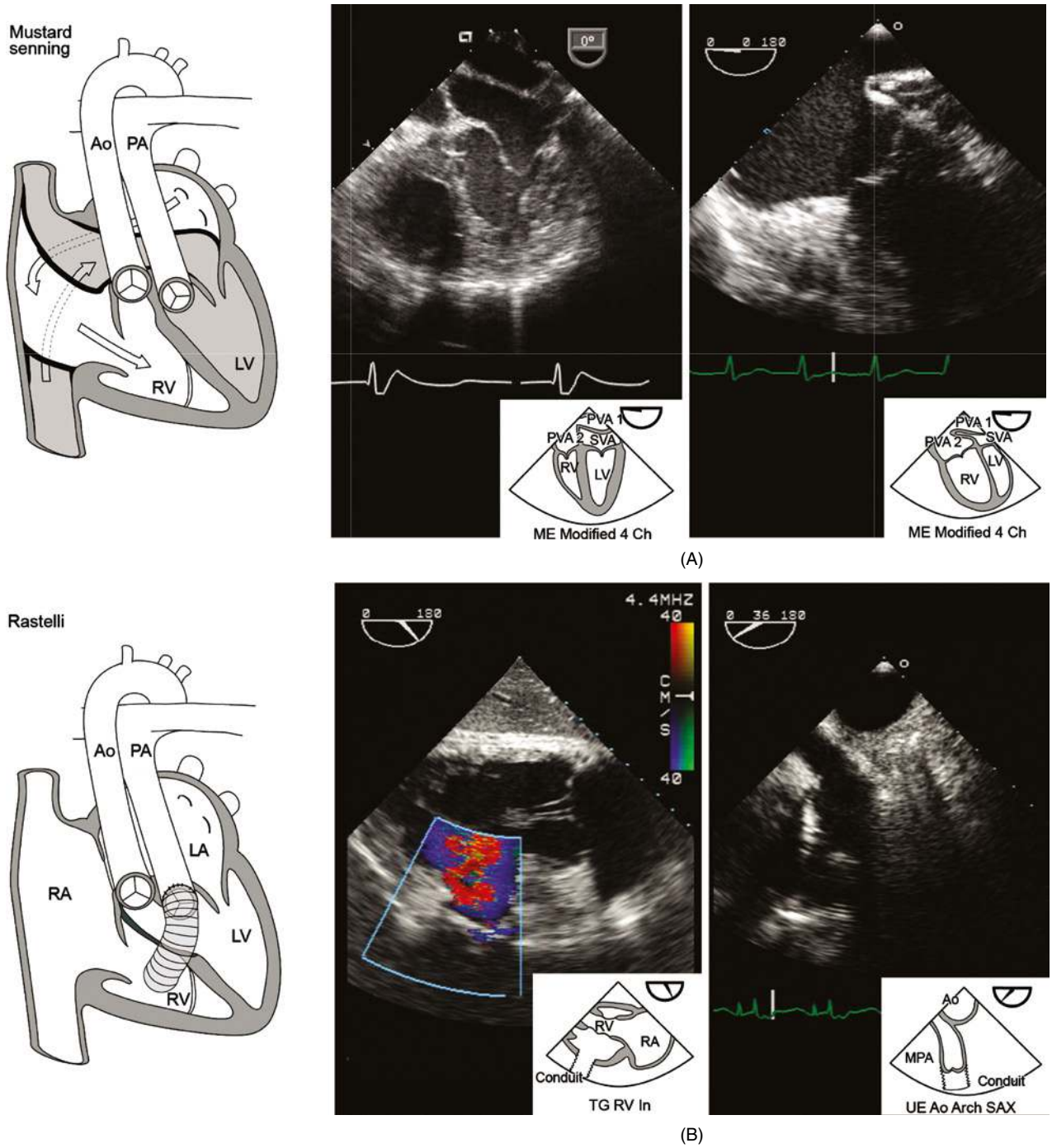


Figure 15.23 *D-Transposition of the great arteries (D-TGA) post-Senning and post-Rastelli operations*. (A) *D-TGA after Senning procedure*. TEE assessment of atrial pathways requires multiple views and sweeps between several planes to trace the course of the blood flows and provide information about atrial anatomy and the presence of baffle pathology (leak or obstruction). *Left panel*: modified ME 4-Ch view depicts the systemic venous atrium (*SVA*), which receives the systemic veins (not shown), and the region of the pulmonary venous atrium where the pulmonary veins drain (*PVA 1*). Note the portion of the baffle that separates the SVA from the PVA 1. *Right panel*: as the TEE probe shaft is turned rightwards, the pathway of pulmonary venous flow can be examined to exclude obstruction from PVA 1 to the region of the pulmonary venous atrium above the tricuspid valve (*PVA 2*). In patients who have undergone atrial baffle procedures, these views in combination with additional TEE cross sections assist in the assessment of systemic right ventricular (*RV*) function, grading severity of tricuspid regurgitation, and evaluating potential intracardiac thrombus related to rhythm abnormalities or pacing leads. (B) *D-TGA post-Rastelli operation*. In the patient with D-TGA and associated ventricular septal defect (VSD) and pulmonary stenosis, a Rastelli-type repair may be favored, where the left ventricular (*LV*) output is re-routed to the aorta (*Ao*) across a VSD patch that serves as a baffle, and an extracardiac conduit is placed between the RV and main pulmonary artery (MPA). *Left panel*: TG RV In view (adult TEE cross section) with color Doppler displays the proximal conduit. *Right panel*: UE Ao Arch SAX view as shown is particularly helpful in the examination of the distal conduit. A combination of TEE modalities that may include 2D, 3D, color, and spectral Doppler in multiple views can assess outflow obstruction, conduit/aortic regurgitation, residual VSD, and estimate RV systolic pressure in the postoperative patient. *LA* left atrium; *PA* pulmonary artery; *RA* right atrium. Diagrams courtesy of Ms. Willa Bradshaw.

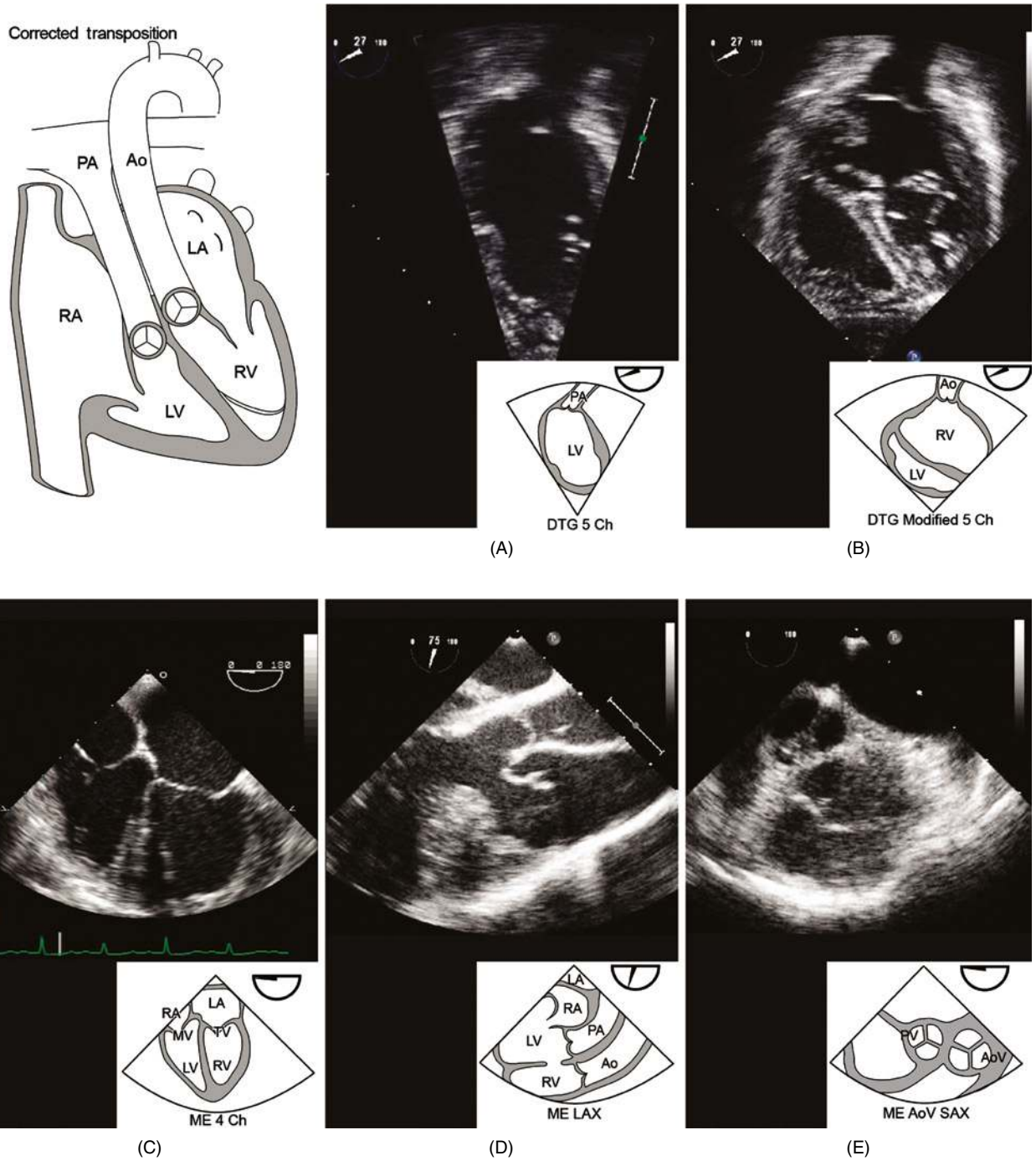


Figure 15.24 *Congenitally corrected transposition (CCTGA)*. (A) *Ventriculoarterial* (*VA*) *discordance* (*left ventricle* [*LV*] *to pulmonary artery* [*PA*] *connection*). The DTG views are essential in the TEE evaluation of CCTGA (also referred to as L-transposition of the great arteries [L-TGA]). The examination requires not only single views but sweeps between planes to assess ventricular morphology, their arrangement, and connections between these and the arterial trunks. The discordant connection between the smooth-walled LV and PA are shown in a DTG view. (B) *VA discordance* (*right ventricle [RV] to aorta* [*Ao*] *connection*). DTG view with anterior probe angulation in the same patient depicted in panel A displays the origin of the Ao from the trabeculated left-sided RV. The smooth-walled LV is to the right of the morphologic RV. (C) *Atrioventricular* (*AV*) *discordance*. Evaluating ventricular morphology and AV connections in CCTGA requires imaging in multiple views at the ME, TG, and DTG levels. As displayed in this ME 4-Ch image, the discordant AV connections are evident as the left atrium (*LA*) opens into a chamber of RV morphology and the right atrium (*RA*) drains into the LV. The identification of the RV is by its trabeculated endocardial surface, the presence of a moderator band, and a septophilic tricuspid valve (*TV*) that is more apically positioned on the interventricular septum relative to the mitral valve (*MV*). The subpulmonary ventricle displays a smooth surface and two papillary muscles (not shown). Various cross sections allow examination of the RV, which often dilates and functions poorly over time, resulting in TV regurgitation. (Source: Vegas [112]. Reproduced with permission of Springer Nature.) (D) *Orientation of the great arteries*. The parallel orientation of the great arteries, with the Ao more anterior, is confirmed in cross sections that display the outflow tracts in their long axes (ME LAX, ME 5-Ch, DTG 5-Ch, and DTG RVOT views). The ME LAX image shown displays this parallel orientation. Note associated pulmonary stenosis (small posterior valvular annulus, stenotic doming leaflets) and the presence of a ventricular septal defect in this case. (E) *Coplanar semilunar valves*. This cardiac lesion makes the aortic valve (*AoV*) and pulmonary (pulmonic) valve (*PV*) appear coplanar (both valves in their short axes seen at the same level), with the PA spatially positioned posteriorly and to the right (in the center of the image), relative to the anterior and leftward Ao. This abnormal orientation is best seen in the ME AoV SAX (shown), ME Asc Ao SAX), and ME RV In-Out views. In this example, the PV appears to have possible commissural fusion. Diagram courtesy of Ms. Willa Bradshaw.

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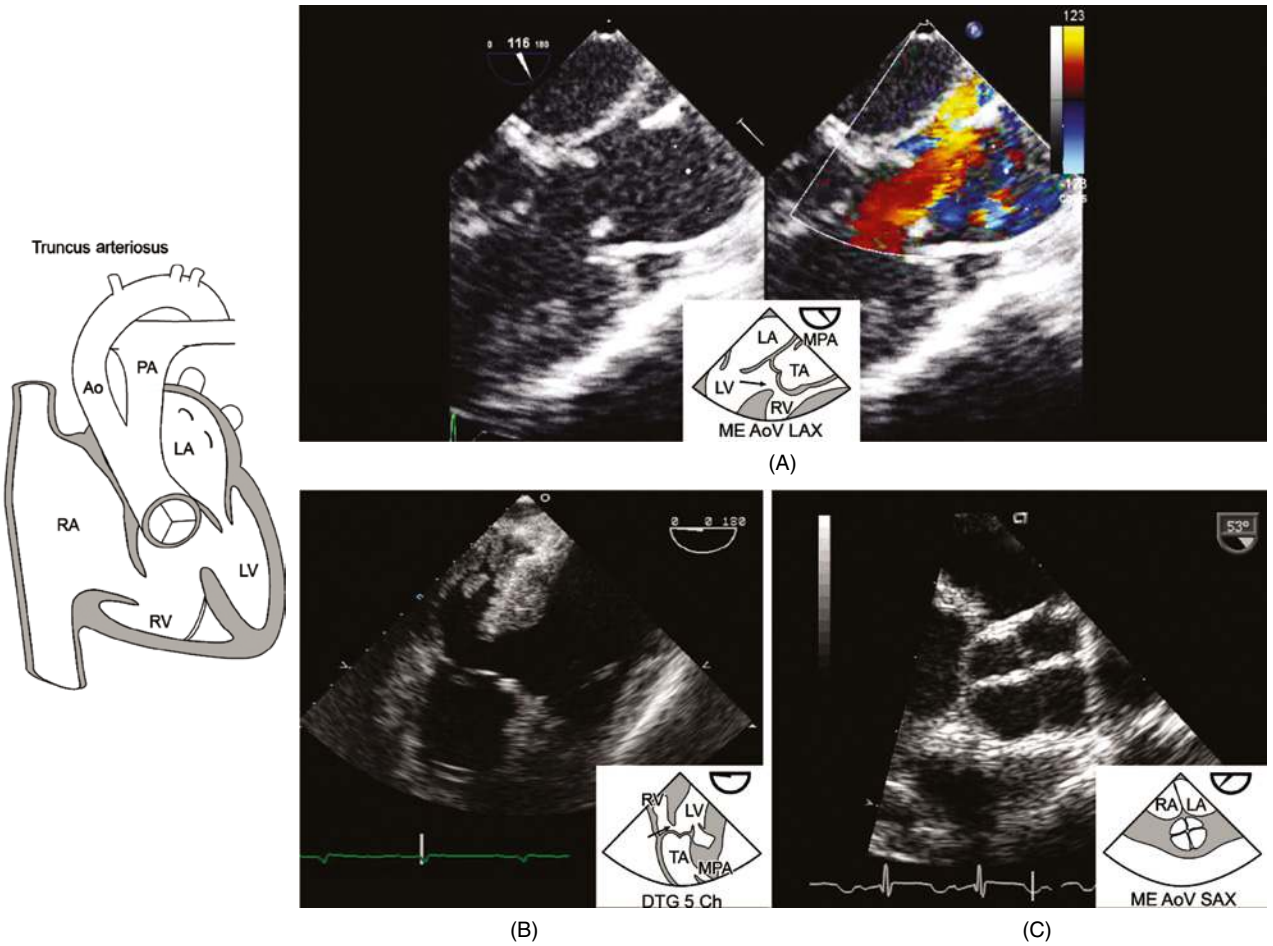


Figure 15.25 *Truncus arteriosus (TA)*. (A) *Truncal root*. The origin and proximal course of the pulmonary arteries (*PAs*) from the arterial trunk can be defined by 2D imaging and color-flow Doppler by adjusting the TEE probe position in the ME Asc Ao SAX, ME Asc Ao LAX (shown), UE PA, and modified UE views. The ventricular septal defect (*arrow*) can also be examined in ME views. (B) *Single outlet*. The assessment of this lesion requires a combination of planes that display the truncal root in short and long axes (ME AoV SAX and LAX), and DTG views. These same cross sections may allow for evaluation of shunting by color and spectral Doppler across the ventricular septal defect. Characteristically a single outlet is identified as displayed in this DTG 5-Ch view (note the nonstandard anatomic orientation of this TEE image with the ventricular apex at the top of the image display and outflow tract at the bottom). (C) *Truncal valve*. Evaluating truncal valve morphology and presence/severity of stenosis and/or regurgitation are important components of the examination. Frequently, a quadricuspid truncal valve is present as shown in this ME AoV SAX view. *Ao* aorta; *LA* left atrium; *LV* left ventricle; *MPA* main pulmonary artery; *RA* right atrium; *RV* right ventricle. Diagram courtesy of Ms. Willa Bradshaw.

aimed at the structural abnormalities and associated hemodynamic and functional alterations. Although rarely diagnostic, an essential aspect of the examination is including views that confirm the anatomic abnormalities. Occasionally, this interrogation reveals new findings or modifies previous ones. Depending on the morphologic substrate, the TEE examination should show the anatomic or functional features that merit a single ventricle management strategy, such as a hypoplastic ventricle with an atretic or severely stenotic inflow or outflow, or a single (common or rudimentary) ventricle with two separate atria that may communicate through an ASD (Figure 15.26). The morphology of the often-enlarged single ventricle may be right, left, or indeterminate. The ME level is suitable for evaluating most of these features. An initial useful cross section is the ME 4-Ch view, which serves as a reference point from which adjusting the multiplane angle optimizes visualization of the various structures of interest. If a patient with a two-ventricle heart is unable to undergo a biventricular repair but instead has a single ventricle management strategy, the examination should identify features of the anatomy that indicate this approach.

In single ventricle variants and two-ventricle hearts not amenable to a biventricular repair, the evaluation of ventricular morphology, size, and function is facilitated by 2D imaging in the ME 4-Ch and ME 2-Ch views, cross sections at the TG and DTG levels, and, if helpful, UE views. Assessment of the AV valves determines their type as single, double, or common and their relationship to the ventricles (straddling and override), patency, and functionality (stenosis or regurgitation). This interrogation is best performed at the ME (4-Ch, 2-Ch, RV In-Out, and Mod Bicaval TV) level. Evaluation of the outflows examines the relation between the ventricles and the arterial roots, their patency, and the semilunar valves. This assessment requires multiple views and

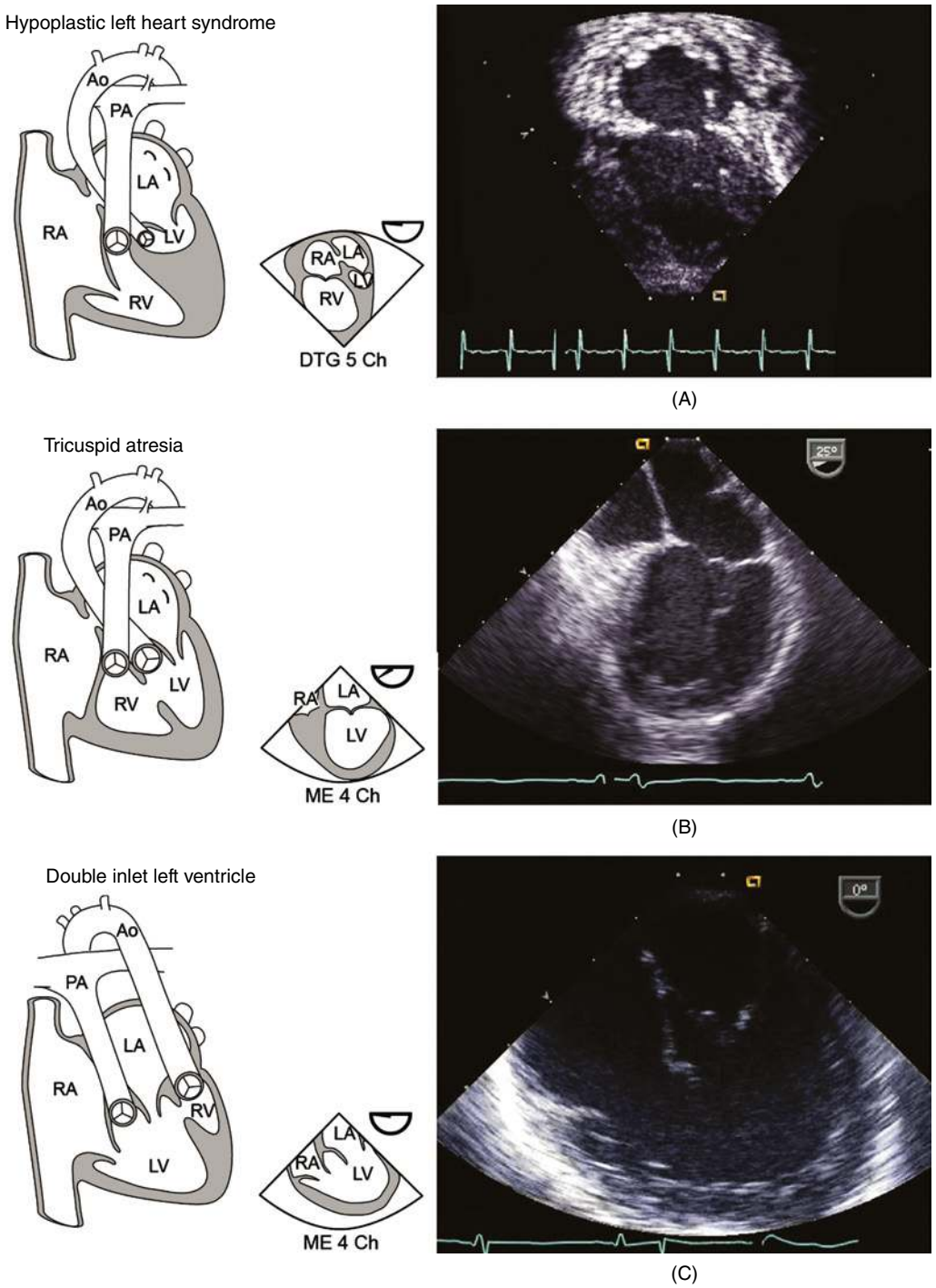


Figure 15.26 *Single ventricle variants*. (A) *Hypoplastic left heart syndrome* (*HLHS*). DTG 5-Ch view showing the characteristic features of HLHS. Note the nonexistent left ventricular (*LV*) cavity, small mitral valve, and tiny left atrium (*LA*). An atrial communication is also seen. (B) *Tricuspid atresia*. ME 4-Ch view displaying the atretic valve in tricuspid atresia and hypoplastic right ventricle (*RV*). (Source Motta and Miller-Hance [199]. Reproduced with permission of Wolters Kluwer Health, Inc.). (C) *Double-inlet left ventricle* (*DILV*). ME 4-Ch view depicting two atrioventricular valves opening into a large ventricular chamber, consistent with the diagnosis of DILV. *Ao* aorta; *PA* pulmonary artery; *RA* right atrium; *RV* right ventricle. Diagrams courtesy of Ms. Willa Bradshaw.

sweeps obtained at the ME (5-Ch, LAX, AoV LAX, AoV SAX, Asc Ao SAX), TG (LAX), and DTG (5-Ch and RVOT views) levels. The adequacy of systemic or pulmonary venous admixture or drainage (ME 4-Ch, ME Bicaval, ME Rt Pulm veins, ME Lf Pulm veins, TG IVC/Hep veins, and DTG Atr Sept views) should also be established. This comprehensive evaluation in the single ventricle patient also requires the use all available Doppler modalities.

Single ventricle surgical management often involves sequential palliative stages. Depending on the anatomy, *stage I palliation* may consist of a surgical technique aimed at providing for or improving systemic (e.g., Norwood procedure)

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or pulmonary blood flow (e.g., systemic to pulmonary artery shunt) or limiting pulmonary overcirculation (i.e., PA banding) to balance pulmonary and systemic blood flows. The *preoperative TEE* examination confirms the anatomy by evaluating the AV and VA connections; AV valve morphology and function; the degree of outflow tract obstruction; size, morphology, and function of the ventricle; and adequacy of the interatrial communication. The *post-CPB TEE* examines the adequacy of the specific intervention, AV valve competence, and ventricular function. *Stage II palliation* usually consists of a bidirectional superior cavopulmonary connection (Glenn shunt or hemi-Fontan procedure). *Postoperative TEE* evaluates patency of the anastomosis, AV valve competence, and ventricular function. The last step or the *stage III operation* is the *Fontan procedure* or *total cavopulmonary connection* using either an intracardiac lateral tunnel or an extracardiac conduit to route blood from the IVC into the PA (Figure 15.27). Creating a fenestration allows blood from the venous system to enter the systemic circulation to maintain CO without depending on passage through the pulmonary circulation. In addition to the anatomic and functional assessment previously mentioned for earlier palliative stages, the *post-CPB TEE* evaluates the Fontan circuit for obstruction, leaks, and patency of any fenestration [14, 220, 221]. There should be low-velocity phasic flows into the PAs and across the Fontan pathway as shown in the ME and DTG views. Spontaneous contrast often appears in the Fontan circuit and represents slow flow along this venous pathway. TEE is particularly helpful in identifying thrombus formation along the Fontan pathway and during cardiac catheterization procedures aimed at creating, enlarging, or occluding a fenestration [222]. Adult patients who have undergone prior Fontan procedures may need revision of the intervention for either thrombotic complications or other problems. The Fontan conversion procedure aims for a more favorable hemodynamic modification.

KEY POINTS: EVALUATION OF SELECTED CONGENITAL HEART DEFECTS BY TEE

- The TEE evaluation of CHD assumes an understanding of the anatomic abnormalities and physiologic repercussions of the various defects.
- The review of information obtained in all prior diagnostic studies, but particularly the TTE findings, is critical before undertaking TEE.
- The comprehensive TEE evaluation in CHD requires the use of all modalities that include 2D and, in selected cases, real-time 3D imaging, spectral Doppler, and color-flow interrogation.
- The examination benefits from the use of multiple TEE planes in all available windows.
- The intraoperative assessment of any defect aims to characterize the abnormalities in question, assess disease severity, and evaluate functional aspects related to the AV valves, semilunar valves, and myocardium, which may affect the clinical course.

Applications of TEE during mechanical support

The options for mechanical circulatory support as a bridge to transplant, and to a lesser extent destination therapy, are growing in CHD populations as experience with these devices increase [223–228]. The spectrum of mechanical support ranges from full support with extracorporeal membrane oxygenation (ECMO) to supporting one or both ventricles with intracorporeal or paracorporeal ventricular assist devices. In addition, some patients with congenital or acquired cardiovascular conditions may benefit from the use of temporary assist devices while cardiac function recovers. Echocardiography plays important roles in the selection, intraprocedural insertion of the device, perioperative management, and postprocedural monitoring in patients with mechanical support [15, 229–236]. Important aspects of the examination are noted in Table 15.10.

Epicardial echocardiography

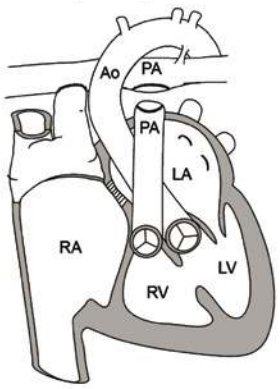
Currently, E-echo is mostly reserved for patients in whom TEE probes cannot be used because of contraindications to esophageal instrumentation (see Table 15.2), size constraints, or the potential for hemodynamic or respiratory compromise, or when TEE hardware is not available. Additional indications for an epicardial study include difficult patient anatomy, poor TEE image quality, and inability to adequately image structures [237–241]. Therefore, E-echo should be considered complementary to TEE in most cases.

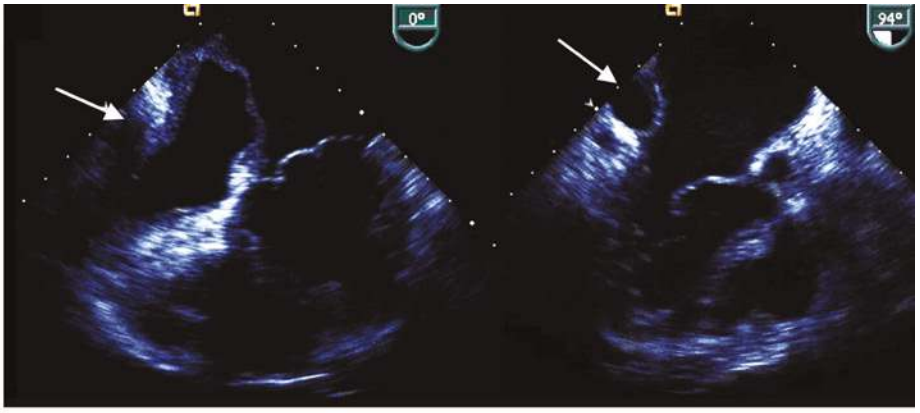
Intraoperative E-echo also provides an alternative technique to image the heart during cardiac surgery and can aid surgical decision-making. Critically ill pediatric patients with an open chest and those on ECMO may also benefit from E-echo in the ICU. In the recent era of the coronavirus disease pandemic, E-echo has been proposed as a possible safer alternative to TEE because it avoids (i) aerosolization, (ii) direct contact between the imaging probe and body fluids (if a probe protective cover is not used), and (iii) the need for special preparation [242].

This technique uses a standard TTE probe placed in a sterile sheath with acoustic gel like that used for percutaneous line insertion [243]. These are lower frequency probes, with good tissue penetration. Image quality can be improved by filling the field with saline or using a saline-filled sterile glove to provide a stand-off between the probe and the structure being imaged. Directly placing the probe on anterior structures like the pulmonary valve provides better image quality than TEE does.

The surgeon or operator manipulates the probe directly on the surface of the heart and great vessels (Figures 15.28 and 15.29). In 2007, the ASE, in conjunction with the SCA, published guidelines for performing a comprehensive E-echo examination and recommended seven views for this examination [244]. The standard views obtained are analogous to standard transthoracic views. In most cases when using this modality in CHD, the imaging examination focuses on addressing specific issues or questions and additional views may be used (Figure 15.30). The freehand

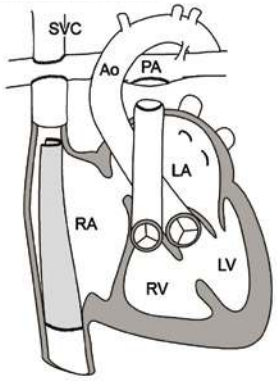
Classic atriopulmonary fontan

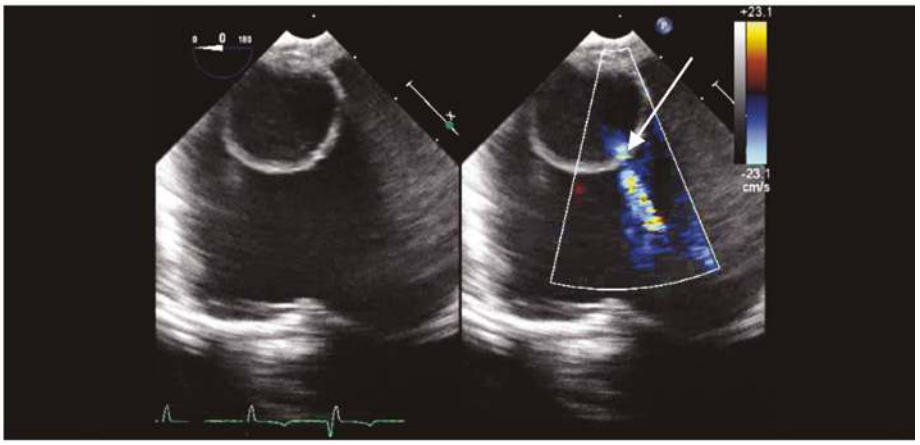




(A)

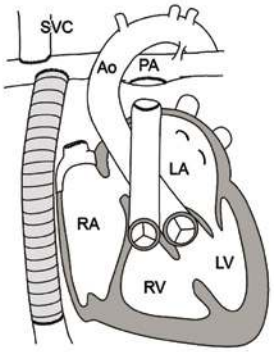
Lateral tunnel fontan

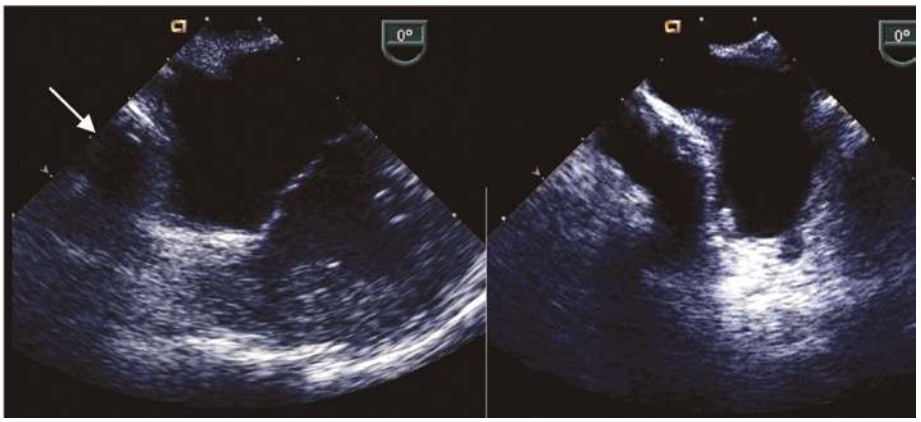




(B)

Extracardiac fontan





(C)

Figure 15.27 *Modifications of the Fontan procedure*. (A) *Classic atriopulmonary connection*. *Left panel*: ME 4-Ch view displays an atriopulmonary Fontan connection in an adult patient with tricuspid atresia depicting a large thrombus (*arrow*) along the free wall of the right atrium (*RA*). Note the RA dilation and bulging of the interatrial septum towards to left atrium (*LA*). *Right panel*: ME 2-Ch view in the same patient showing a dilated coronary sinus (*arrow*) due to high RA pressures. (B) *Lateral tunnel Fontan connection*. *Left panel*: zoomed ME 4-Ch view of a lateral tunnel Fontan connection (circular structure in the atrium). *Right panel*: corresponding color Doppler image depicting right-to-left shunting across the Fontan fenestration (arrow). By allowing for venous blood to enter the common atrium, this maintains cardiac output at the expense of arterial desaturation. (C) *Extracardiac Fontan connection*. *Left panel*: ME 4-Ch view shows the extracardiac conduit (*arrow*) allowing inferior vena cava blood to enter the pulmonary artery (*PA*) in a patient after a prior Glenn procedure, thereby achieving a total cavopulmonary connection. *Right panel*: as the TEE probe is rotated rightwards, the extracardiac conduit can be further displayed longitudinally in a zoomed image. Obstruction to flow across the right-sided pulmonary veins, related to the conduit, should be excluded after Fontan completion. *Ao* aorta; *LV* left ventricle; *RV* right ventricle; *SVC* superior vena cava. Diagrams courtesy of Ms. Willa Bradshaw.

Table 15.10 Parameters to be evaluated by transesophageal echocardiography during ventricular assist device surgery

LVAD		RVAD
Pre-insertion (STARR criteria) • Intracardiac **S**hunts • Intracardiac **T**hrombi • Ascending Aorta Pathology • **A**ortic Regurgitation (≥ mild) • Mitral Stenosis (≥ mod) • T**R** (≥ mod), TS (> mild) • **R**ight Ventricular Function	**Post-insertion** *During weaning* • Intracardiac air • RV function • LV decompression • IVS position *After weaning* • Inflow cannula • Outflow cannula • Intracardiac shunts • Aortic valve opening • Aortic insufficiency • Tricuspid regurgitation • RV Function	**Pre-insertion** • Pulmonary regurgitation • LV function • Thrombi (RA, RV, PA) **Post-insertion** • Inflow cannula • Outflow cannula • Pulmonary regurgitation • RV decompression • LV size and function

Abbreviations: *IVS* interventricular septum; *LV* left ventricle; *LVAD* left ventricular assist device; *PA* pulmonary artery; *RA* right atrium; *RV* right ventricle; *RVAD* right ventricular assist device; *TR* tricuspid regurgitation

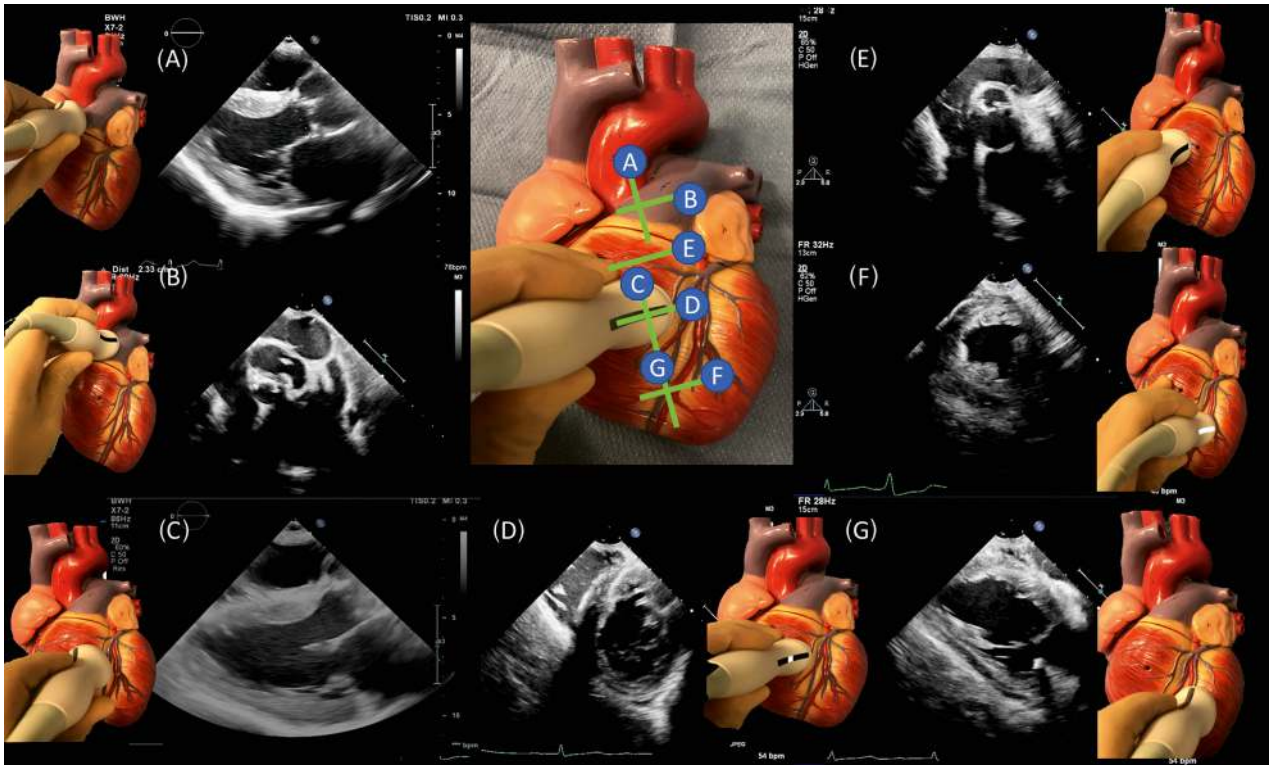


Figure 15.28 *Standard epicardial echocardiography views*. Similar to transthoracic echocardiography, for epicardial imaging the probe is positioned on the surface of the heart with the probe marker pointing cephalad or to the left of the patient. Most views are orthogonal to each other, so obtaining a long- or short-axis view and rotating the probe 90° shows the other view at the same heart level. Slight tilting and rotation of the probe can help optimize each view. (A) *Aortic valve (AoV) long-axis (LAX) view*. The probe position aligns parallel to the long axis of the ascending aorta with the marker pointing cephalad. This view shows the AoV and left ventricular outflow tract (LVOT) permitting color and spectral Doppler interrogation. (B) *AoV short-axis (SAX) view*. The probe is rotated 90° clockwise from the AoV LAX view with the probe marker to the patient's left. This view shows the short axis of the aortic root at the level of the aortic sinuses. (C) *Left ventricular (LV) LAX view*. The probe is positioned in the middle of the right ventricular (RV) free wall aligned with the long axis of the Ao with the marker pointing cephalad. This view shows the entire LV in long axis and mitral valve. (D) *LV basal SAX view*. The probe is rotated 90° clockwise from the LV LAX view with the probe marker pointing leftward, until the MV leaflets appear in short axis ("fish-mouth" view) and the RV is in the near-field with the tricuspid valve on the left of the image. (E) *RV inflow-outflow view*. The probe is positioned over the RV outflow tract (RVOT) with superior angulation and the probe marker to the left. The RVOT appears in the near-field, the AoV in the center, the pulmonary valve (PV) in long axis on the screen right, and the proximal main PA below. This view allows for color-flow Doppler assessment of the PV and depending on angle alignment, may facilitate measurements of RVOT and PV gradients. (F) *LV mid-SAX*. From the LV basal SAX view, angulation or moving the probe inferiorly with the probe marker to the left, displays the LV in SAX at the level of the papillary muscles. (G) *LV two-chamber* view. The probe is rotated 90° counter-clockwise from the LV mid-SAX view with the probe marker pointing cephalad, shows the long axis of the LV.

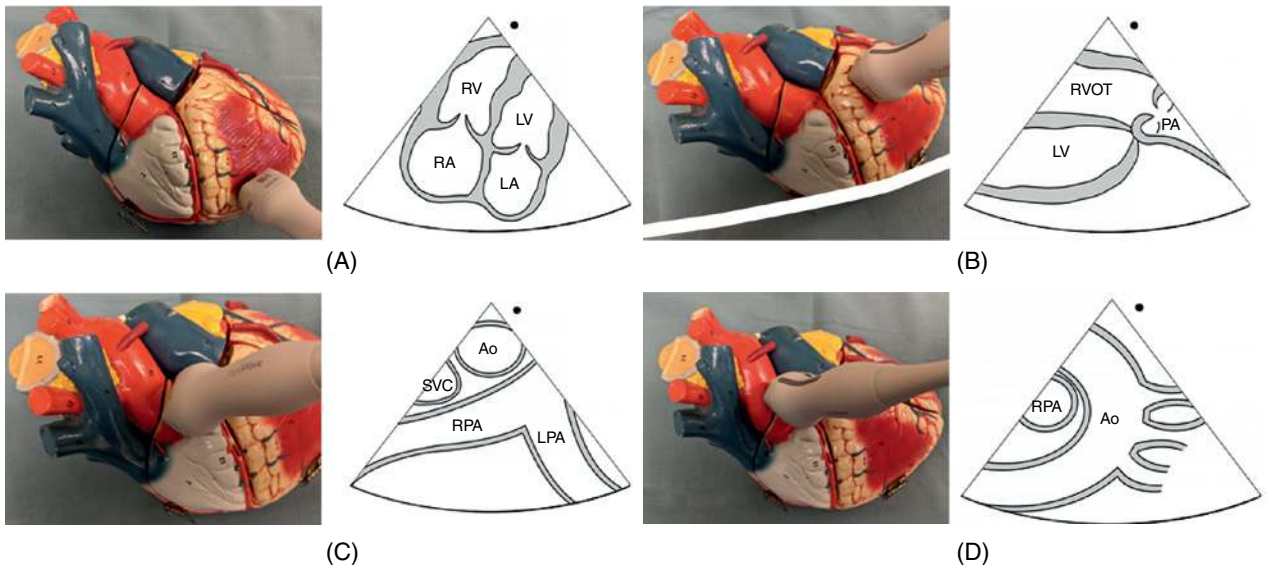


Figure 15.29 *Additional epicardial echocardiography views in congenital heart surgery*. (A) *Subxiphoid equivalent modified apical four-chamber view*. By positioning the probe over the inferior border of the right ventricle (RV) with slight clockwise rotation and the marker pointing to the left, a modified four-chamber view is obtained as shown allowing for visualization of the RV, left ventricle (LV), left atrium (LA), right atrium (RA), interatrial septum, a portion of the interventricular septum, as well as assessment of atrioventricular valve function. (B) *RV outflow tract view*. The probe is positioned over the RV outflow with the marker pointing to the patient's left shoulder. The view shows the right ventricular outflow tract (RVOT), pulmonary valve, main pulmonary artery (PA), and a portion of the LV. (C) *Branch PA view*. The probe is positioned over the ascending aorta or main pulmonary artery bifurcation, with the marker pointed to the left shoulder. The view images the main and branch pulmonary arteries. (D) *Aortic arch view*. The probe is positioned over the distal ascending aorta (Ao) aligned along the long axis of the aortic arch with the marker pointed to the patient's left. This view shows the aortic arch and arch vessels. *LPA* pulmonary artery; *RPA* right pulmonary artery; *SVC* superior vena cava.

manipulation of the probe by the operator permits off-axis imaging to evaluate the anatomic variations unique to each CHD patient. Color-flow Doppler can assess the surgical result. Visualizing all four chambers and valves of the heart, as well as the great vessels, is feasible in most patients, although apical views may not be obtainable. Structures that are particularly well imaged with E-echo include the aortic arch, branched pulmonary arteries, and coronary vessels. Recent reports suggest that 3D epicardial imaging is beneficial in CHD [245].

Drawbacks of E-echo relate to the risk of infection and the consequent need for sterility, limited windows of interrogation, interruption or distraction from the surgical procedure, and the need for a skilled operator. Furthermore, compression of structures during E-echo can cause arrhythmias and hemodynamic instability. In the operating room, a second, unsterile operator is needed to operate the ultrasonography machine and archive the images. Cooperation among the operative team is essential for the safe incorporation of this practice into the procedural workflow.

Summary

Over the years, TEE has become a valuable adjunct to surgical, hemodynamic, and anesthetic management in the patient with CHD. In the intraoperative setting, TEE confirms the diagnosis, facilitates planning or refinements of the intervention, and immediately evaluates the operative results. TEE can detect suboptimal surgical results or complications, thereby often preventing the need for subsequent reoperations and reducing overall morbidity, mortality rates, and costs. The contributions of TEE to anesthetic care include real-time monitoring of ventricular filling and cardiac function, ensuring adequate cardiac de-airing, and facilitating the optimization of hemodynamic management strategies. In the cardiac catheterization laboratory, TEE provides guidance of interventional procedures, assesses the success of the intervention, identifies complications, and enhances overall patient safety.

The overview presented in this chapter regarding the contributions of TEE in patients with CHD reflects the impact of the technology on clinical care and its positive influence on outcomes. Most centers consider the TEE imaging approach as the standard for intraoperative assessment during cardiac surgery and many interventions in the cardiac catheterization laboratory. As TEE technology continues to evolve, additional applications and contributions will probably be recognized for both children and adults with CHD. Epicardial imaging is now a well-established intraoperative option in patients in whom TEE is not feasible or when additional information is necessary by using this imaging approach as a complement to TEE.

Acknowledgments

We would like to acknowledge Ms. Willa Bradshaw, BSc, MScBMC, and Ms. Elizabeth (Beth) E. Sumner, MA, medical illustrators, for their outstanding graphic contributions to this chapter. We also thank Stephen N. Palmer, PhD, ELS, of the Department of Scientific Publications at the Texas Heart Institute for his editorial assistance.

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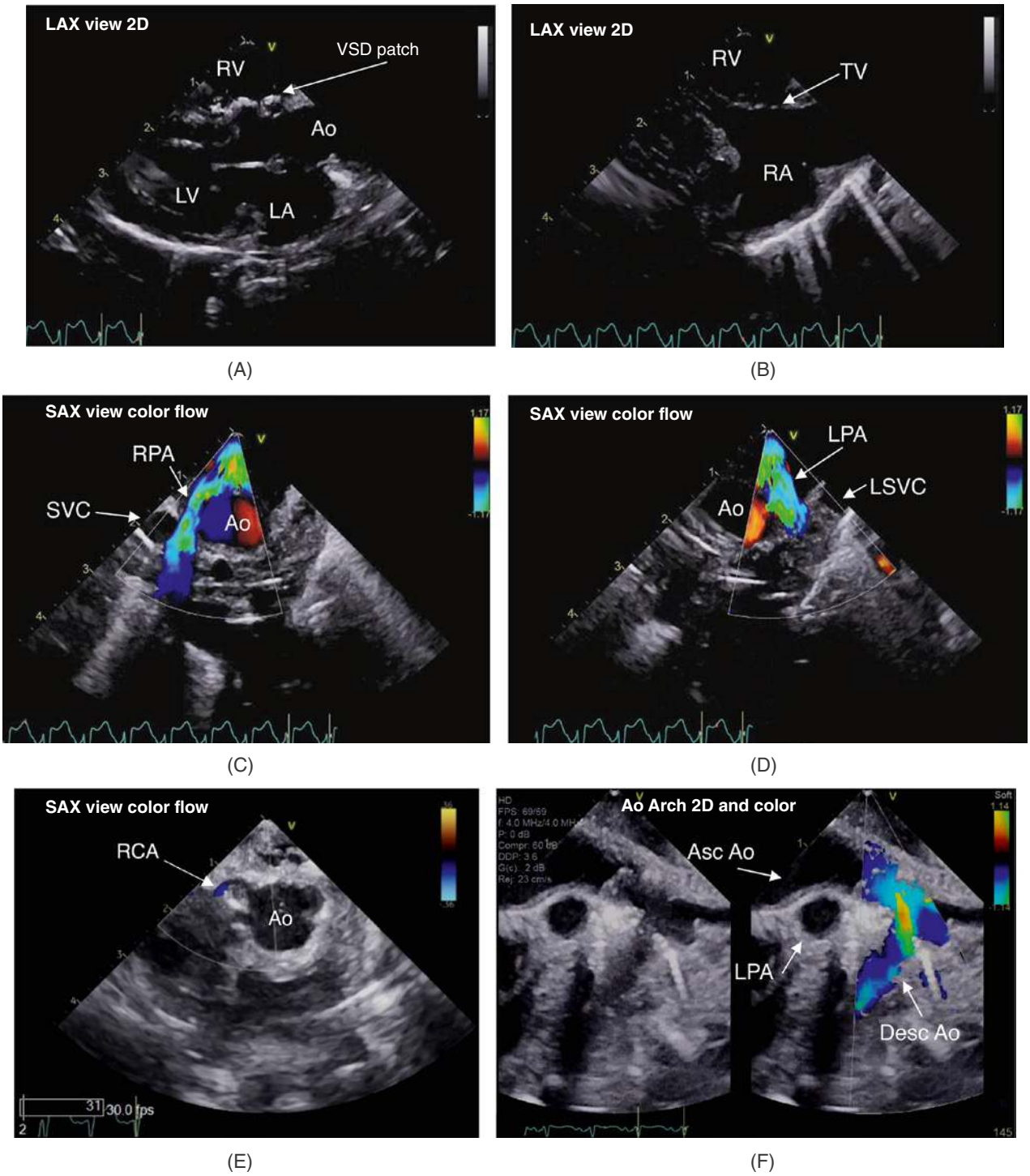


Figure 15.30 *Epicardial imaging in congenital heart disease*. (A) Long-axis (LAX) 2D view showing the left ventricle (LV), left atrium (LA), right ventricle (RV), and aorta (Ao) after pericardial patch closure of ventricular septal defect (VSD; arrow). (B) Interrogation of the right ventricular inflow in a long-axis (LAX) view, as the transducer is angulated rightward and inferiorly with respect to the view shown in panel A, shows the right atrium (RA), right ventricle (RV), and tricuspid valve (TV). (C) and (D) Branch pulmonary artery view (note short-axis [SAX] views of aortic root) obtained following an arterial switch operation in a neonate with transposition of the great arteries display draping of the right pulmonary artery (RPA) and left pulmonary artery (LPA) over the Ao in the respective images. Note the relationship of the superior vena cava (SVC) to the right of the Ao and persistent left superior vena cava (LSVC) to the left. (E) In the same patient as shown in panels C and D, the graphic displays the right coronary artery (RCA) after being translocated to the neoaorta (Ao) as interrogated by color-flow Doppler. (F) 2D and color Doppler imaging of the Ao arch following coarctation repair.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Hahn RT, Abraham T, Adams MS, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:921–64. Updated and most recently published ASE-SCA guidelines for performing a comprehensive TEE examination. The publication focused on the adult patient with a structurally normal heart.

4 Simpson J, Lopez L, Acar P, et al. Three-dimensional echocardiography in congenital heart disease: an expert consensus document from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2016;17:1071–97. Comprehensive document reviewing applications, image orientation, and technical considerations of 3D imaging in congenital heart disease.

5 Puchalski MD, Lui GK, Miller-Hance WC, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination in children and all patients with congenital heart disease: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32:173–215. Guidelines document by the ASE outlining indications, safety issues, and training requirements for the performance of a TEE examination in the patient with CHD.

15 Nicoara A, Skubas N, Ad N, et al. Guidelines for the use of transesophageal echocardiography to assist with surgical decision-making in the operating room: a surgery-based approach: from the American Society of Echocardiography in Collaboration with the Society of Cardiovascular Anesthesiologists and the Society of Thoracic Surgeons. J Am Soc Echocardiogr 2020;33:692–734. Outstanding recently published document that outlines in systematic manner the use of TEE in specific surgical settings.

28 Wong PC, Miller-Hance WC. Transesophageal Echocardiography for Pediatric and Congenital Heart Disease. 2nd ed. London: Springer, 2021, p. 826. Comprehensive contemporary textbook that focuses exclusively on the clinical applications of TEE in children and the pediatric and adult population with CHD.

83 Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:3–46. This publication provides a practical guide on using 3D echocardiography and addresses the limitations of the technique, as well as current and potential clinical applications.

112 Vegas A. Perioperative Two-Dimensional Transesophageal Echocardiography: A Practical Handbook, 2nd ed. Cham, Switzerland: Springer, 2018, p. 338. A compact, practical handbook that serves as a portable guide for the use of perioperative TEE.

123 Reeves ST, Finley AC, Skubas NJ, et al. Basic perioperative transesophageal echocardiography examination: a consensus statement of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:443–56. This paper describes the role of a basic TEE examination in the care and treatment of an unstable patient in the intraoperative setting.

186 Williams T, Lluri G, Boyd EK, Kratzert WB. Perioperative echocardiography in the adult with congenital heart disease. J Cardiothorac Vasc Anesth. 2019;34:1292–308. Review article focusing on current international consensus recommendations on echocardiographic imaging of adults with CHD.

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CHAPTER 16

Coagulation, Cardiopulmonary Bypass, and Bleeding

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Introduction

Pediatric cardiac surgery is associated with a substantial risk of bleeding, frequently requiring the administration of allogeneic blood products. The anemia and coagulopathy observed in neonates and children perioperatively are complex and multifactorial. Efforts to optimize preoperative hemoglobin, understand and correct coagulopathy, and incorporate blood conservation strategies to reduce bleeding are integral parts of pediatric cardiac anesthesiology and surgery. In this chapter, we will begin by reviewing the coagulation pathway, its maturation, and alterations associated with the pathophysiology of congenital heart defects (CHD). We will address preoperative optimization and blood conservation techniques, issues involved with the management of the coagulation system during and after cardiopulmonary bypass (CPB), and modalities for treating coagulopathy and bleeding in the perioperative period.

Coagulation

Mechanisms of hemostasis

Hemostasis is a complex physiologic process that regulates the formation and dissolution of a fibrin network through (i) platelet activation and aggregation, (ii) thrombin generation and fibrin clot formation, and (iii) fibrinolysis. The normal hemostatic mechanism that is triggered after vascular injury initiates a complex cascade of biochemical signaling and interactions between platelets, coagulation proteins, proteolytic enzymes, and fibrinolytic mechanisms. All of these actions are tightly regulated so that clotting occurs only at the site of vascular injury while maintaining blood flow in other parts of the circulation. The three phases of hemostasis are (i) primary hemostasis (formation of the platelet plug), (ii) secondary hemostasis (coagulation), (iii) tertiary hemostasis (fibrinolysis) (Figure 16.1).

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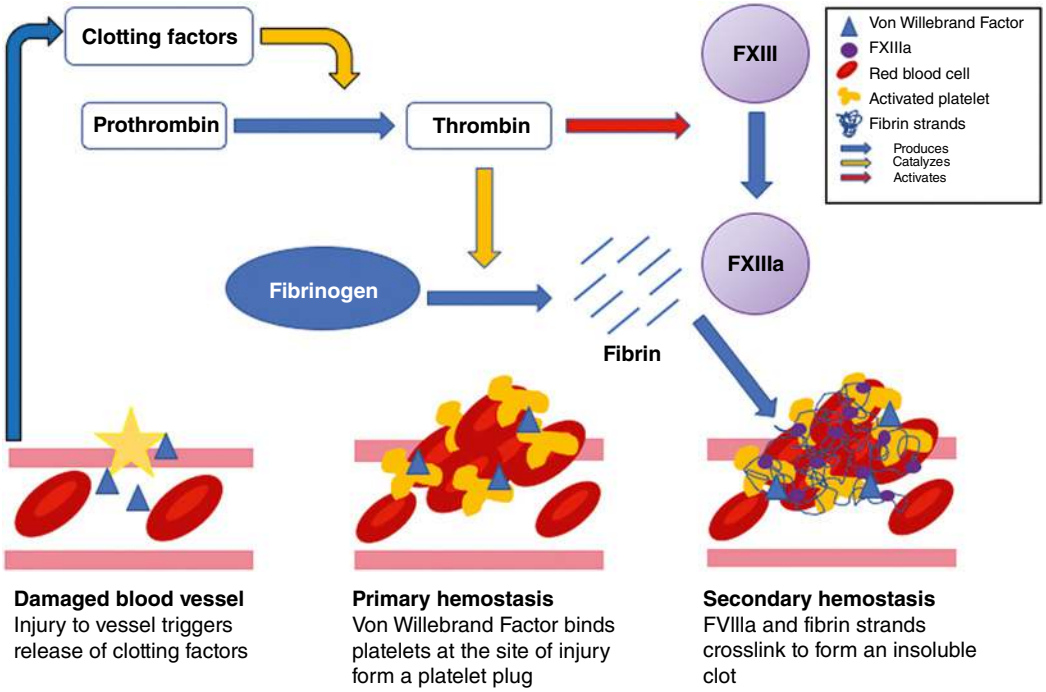


Figure 16.1 Simplified mechanisms of hemostasis including primary hemostasis and secondary hemostasis.

Primary hemostasis

Primary hemostasis reduces bleeding after vessel damage by inducing vasoconstriction at the site of injury and initiating platelet adhesion, activation, and aggregation to form a platelet plug. First, damage to the blood vessel walls exposes subendothelial collagen, which then binds circulating von Willebrand factor (vWF). Platelets *adhere* to the exposed vWF via glycoprotein 1b (GPIb) receptor on platelet surfaces. The binding of platelets to the subendothelial collagen-vWF complex triggers platelet *activation*. Upon activation, platelets release thromboxane A2 (TXA_2) and adenosine diphosphate (ADP) from their granules. These hemostatic mediators strengthen interactions between adherent platelets and promote the recruitment of additional circulating platelets to the growing platelet plug. Subsequently, negatively charged phospholipids are expressed on the surface membrane of activated platelets, which create an active surface on which coagulation proteins interact. Finally, the platelet glycoproteins GpIIb/IIa are converted to the active form and bind both fibrinogen and vWF to promote aggregation. The process of platelet *aggregation* is further modulated by the microenvironment. At low shear rates, platelet aggregation occurs predominately via $(alpha)_{IIb}ß_3$ integrin and fibrinogen interactions, while at higher shear rates, platelets aggregate increasingly in a vWF-dependent manner. Further aggregation and platelet plug development occur as surrounding platelets are activated by serotonin, TXA2, and ADP released by other platelets [1]. This local process is tightly controlled to prevent the propagation of the platelet plug beyond the site of injury by power platelet aggregation inhibitors and vasodilators produced by non-injured endothelial cells.

Secondary hemostasis

Secondary hemostasis leads to the formation of a fibrin clot by sequentially activating circulating coagulation factors to finally form insoluble fibrin. Our understanding of this "coagulation cascade" has evolved from the traditional description of independent "intrinsic" and "extrinsic" pathways being activated in plasma to a "cell-based" concept of coagulation factors interacting on the surface of tissue factor (TF)-bearing cells and activated platelets at the site of vascular injury [2].

The cell-based model describes three overlapping phases of coagulation: *initiation* of coagulation factors on TF-bearing cells, *amplification* of coagulation by thrombin generated on these TF-bearing cells, and *propagation* of thrombin generation on platelet surfaces. TF, exposed in the vascular subendothelium after injury, is the primary physiologic initiator of coagulation [2].

Initiation of coagulation occurs when plasma factor VII (FVII) binds tightly to TF and is rapidly activated to FVIIa. This FVIIa-TF complex catalyzes the activation of coagulation factors, FX and FIX. The FXa on the surface of TF-bearing cells binds with FVa to produce small amounts of thrombin (II). This initial amount of thrombin, though insufficient to initiate fibrin formation, plays an important role in subsequently activating platelets and FVIII during the amplification phase [2].

During the *amplification* phase, the small amount of thrombin generated on TF-bearing cells amplifies the initial procoagulant signal by enhancing platelet adhesion, activating platelets, and activating factors V, VIII, and XI. Thus, thrombin acts on the platelet surface to "set the stage" for procoagulant complex assembly [2]. On the activated platelet surface, FIXa joins with FVIIIa to form the "tenase" complex (FVIIa/FIXa). The complex activates large amounts of FXa which joins with

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its cofactor, FVa, to form the "prothrombinase" complex (FXa/FVa). During the *propagation* phase, the "tenase" and "prothrombinase" complexes are assembled on the platelet surface to generate a large-scale conversion of prothrombin into thrombin. Unlike the small amount of thrombin produced in the initiation phase, this quantity of thrombin is sufficient to cleave fibrinogen to fibrin strands that are necessary for clot formation [2].

Tertiary hemostasis

The final phase of hemostasis, termed *fibrinolysis*, involves fibrin clot maturation and fibrinolysis. Activated factor XIII cross-links the fibrin monomers and acts as "mortar" that cements the platelet plug to form a stable clot. After clotting has occurred and bleeding has stopped, activation of the fibrinolytic system breaks down the thrombus in order to re-establish normal blood flow. Circulating plasminogen binds to fibrin within the clot. Tissue plasminogen activator (tPA) released from endothelial cells also complexes with fibrin and converts the bound plasminogen to its active form, plasmin, leading to the enzymatic dissolution of the thrombus. This stage is critical to maintaining and restoring the patency of the involved blood vessel so that blood flow can be restored, and wound healing can proceed.

Hemostatic homeostasis

The hematological system constantly balances the ability to keep blood flowing through undamaged vessels with the ability to stop bleeding from damaged blood vessels. Under normal circumstances, blood vessels are non-thrombogenic because of intact endothelial surfaces and circulating activated protein C, with its cofactor protein S inactivating any circulating FVa and FVIIIa to attenuate thrombin generation. Antithrombin (AT) neutralizes circulating FXIa, FXa, FXIa, and thrombin to prevent fibrin formation. Circulating nitric oxide and prostacyclin inhibit platelet activity and release tPA to promote fibrinolysis. Thus, clot formation is prevented in undamaged blood vessels while vascular damage disrupts these homeostatic mechanisms to create an environment conducive to clot formation. Furthermore, when vascular damage does occur, the coagulation process is restricted only to the injured vessels because the coagulation process-inducing TF is expressed on damaged vessels and also because a host of circulating anticoagulants keeps the actions circulating activated coagulation factors in check. Under normal conditions, coagulation and fibrinolysis occur only where they are needed and are prevented from becoming pathological generalized problems by procoagulant and anticoagulant factors that delicately balance the system.

KEY POINTS: MECHANISMS OF HEMOSTASIS

- Primary hemostasis involves platelet adhesion, activation, and aggregation to form a platelet plug at the site of injury.
- Secondary hemostasis involves coagulation factor activation and fibrin clot formation.
- Tertiary Hemostasis involves cross-links of fibrin strands and break down of the clot through fibrinolysis.

Developmental hemostasis

Like most organ systems in the newborn, the hematologic system is not fully developed at birth but matures over the first year of life. In the late 1980s, Dr. Maureen Andrew termed the age-related changes of the hemostatic system *developmental hemostasis* [3]. This parallel maturation of the coagulation and fibrinolytic systems maintains the delicate hemostatic balance between thrombosis and bleeding in healthy neonates and infants. An understanding of these changes in the coagulation system is critical for practitioners involved in caring for pediatric cardiac patients.

Although maternal coagulation factors do not cross the placenta, the synthesis of coagulation proteins begins at approximately 11 weeks gestation. Levels of coagulation factors are dependent on the gestational age of the neonate, with major increases in both procoagulant and anti-coagulant factors occurring between 30 and 40 weeks of gestation and reaching adult levels by 1 year of age [3–5]. In contrast, levels of fibrinogens, FV, VIII, FXIII, vWF, and platelet counts are comparable to adult values on the first day of life. In addition to these quantitative differences, recent studies have demonstrated qualitative differences in several hemostatic components, which manifest throughout the three stages of hemostasis (Table 16.1).

Platelet counts in neonates are similar to those found in older children and adults, but neonatal platelets show a qualitative decrease in function for the first 2–4 weeks of life. However, the literature regarding neonatal platelet function is conflicting, with some studies demonstrating platelet hyporeactivity and others demonstrating accelerated coagulation [6–13]. The *in vitro* activation of neonatal platelets is decreased to a variety of standard agonists including

Table 16.1 Differences in coagulation components between neonates and adults

Component	Neonatal versus adult levels
Primary hemostasis	←→ Platelet Count
	↑ vWF
Coagulation factors	↓ FII, FVII, FIX, FX
	↓ FXI, FXII
	↓ to ←→ FVI, FXIII
	←→ Fibrinogen
	↑ FVIII, vWF
Anticoagulation factors	↓ PC, PS, AT, TFPI
	↑ alpha2M
Fibrinolysis	↓ Plasminogen
	↓ to ←→ PAI

vWF = von Willebrand factor; F = factor; TFPI = Tissue factor pathway inhibitor; AT = antithrombin; PC = Protein C; PS = Protein S; alpha2M = alpha2-macroglobulin; PAI = Plasminogen activator inhibitor.
Source: Adapted from Anderson et al. [3–5].

epinephrine, ADP, collagen, and thrombin [10, 14]. This hyporeactivity manifests in several ways: (i) a decrease in platelet granule secretion; (ii) decreased expression of fibrinogen-binding sites on platelet surfaces; (iii) deficiencies in neonatal phospholipid and calcium metabolism that impair platelet activation; and (iv) immature signal transduction pathways and reduced platelets surface receptors that impair platelet aggregation [6, 15]. As such, Caparros-Peres and colleagues report *reduced* platelet adhesion and aggregation in a plasma-free medium [11]. Despite the impaired function in *in vitro*, most *in vivo* assays of platelet function show adequate neonatal platelet function. For example, bleeding time (BT) and platelet closure time (PFA-100) have been shown to be shorter than adults, suggesting *increased* adhesion and aggregation [12]. Similarly, viscoelastic testing often demonstrates normal or accelerated coagulation in this population [7]. Interestingly, when adult platelets were placed into neonatal blood, bleeding times were dramatically shorter when compared with adult platelets added to adult blood [13]. These *in vivo* assays may be explained by the prominent role that plasma proteins play in neonatal hemostasis. In fact, neonates have a higher concentration of plasma vWF and a greater percentage of the ultra-large vWF necessary for improved platelet adhesion. Despite these conflicting studies, primary hemostasis appears to remain intact in healthy neonates and children.

At birth, many of the coagulation factors involved in secondary hemostasis are quantitatively lower than adults. In newborns, mean levels of the vitamin K-dependent procoagulant factors (II, VII, IX, X) and contact factors (XI, XII, PK, and HMWK) are about 70% of adult levels (Figure 16.2) [3]. This can be attributed to the immature fetal liver, which has reduced ability to provide the gamma-carboxylation needed to produce vitamin K-dependent factors [16]. This is partially counterbalanced by higher levels of vWF and ultra-large vWF, which improve adherence between platelets and injured vessels [17] (Figure 16.3). Neonatal hemostasis is balanced by having concurrent lower levels of the anticoagulants antithrombin (AT), Protein C, and Protein S, and fibrinolytic factors (plasminogen and tPA) (Figure 16.4) [3–5]. The higher levels of thrombin inhibitor alpha2-macroglobulin counteract lower levels of other anticoagulants. In the presence of these quantitative and qualitative factor deficiencies, neonates tend to generate significantly less thrombin than adults.

In addition to lower levels of clotting factors, the existence of neonatal forms of clotting proteins has been described. Most notably, Brown and colleagues demonstrated an immature form of fibrinogen [18], which has differing phosphorus and sialic acid content than adult fibrinogen [19]. These differences lend unique properties to the differences in clot formation between neonatal and adult fibrinogen [18, 20]. Clots formed from adult fibrinogen display higher fiber density and significant three-dimensional branching structure. In contrast, clots formed from neonatal fibrinogen display a more linear, two-dimensional structure with increased porosity and less branching [18]. Clots formed from neonatal fibrinogen display a significantly faster degradation rate than their adult fibrinogen counterparts [18]. However, when adult and neonatal fibrinogen are mixed, simulating a transfusion event, neonatal and adult fibrinogen do not integrate completely during the process of fibrin formation (Figure 16.5). Even more concerning, these mixed clots have a slower degradation time than clots formed from neonatal fibrinogen alone. This data suggests neonatal clots may be more susceptible to fibrinolysis, but differences in the neonatal fibrinolytic proteins may help maintain the hemostatic balance.

Tertiary hemostasis mainly involves the breakdown of the fibrin clot by plasmin. Neonatal plasminogen levels are about 25–50% of adult levels until about 6 months of age [21, 22]. Since plasminogen's *in vivo* activator, tPA, is comparably low in neonates, the rate of conversion from plasminogen to plasmin is also decreased in neonates relative to adults. In contrast, the activity of plasminogen activator

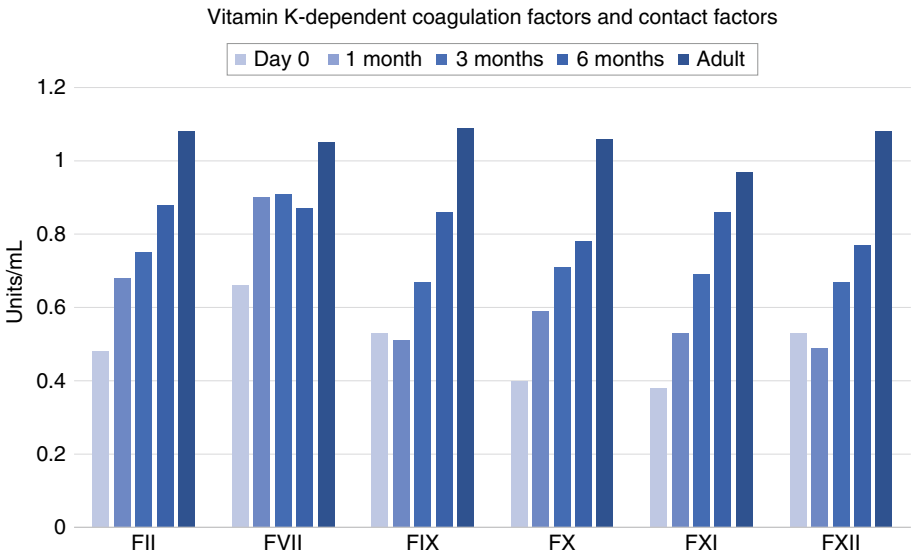


Figure 16.2 Vitamin K-dependent coagulation factors and contact factors in full-term infants through adulthood. F = factor. (Source: Adapted from Andrew et al. [5].)

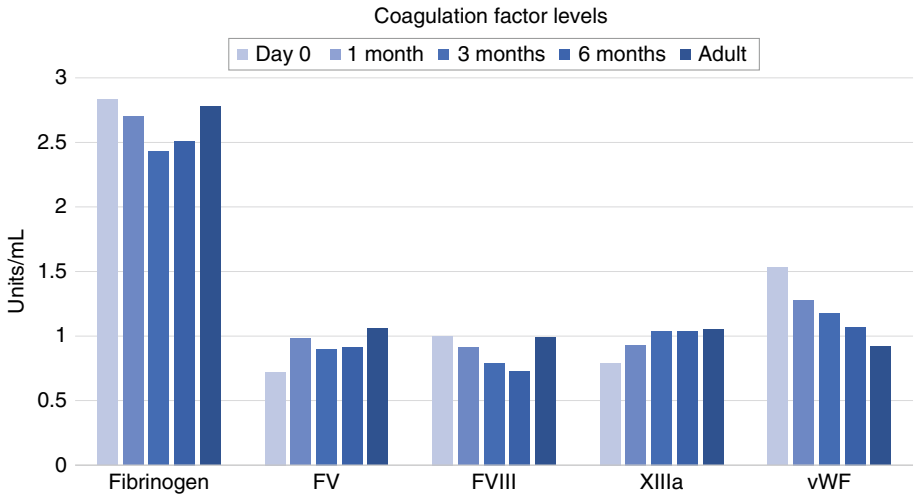


Figure 16.3 Coagulation factors in full-term infants through adulthood. F = factor; vWF = von Willebrand Factor. (Source: Adapted from Andrew et al. [5].)

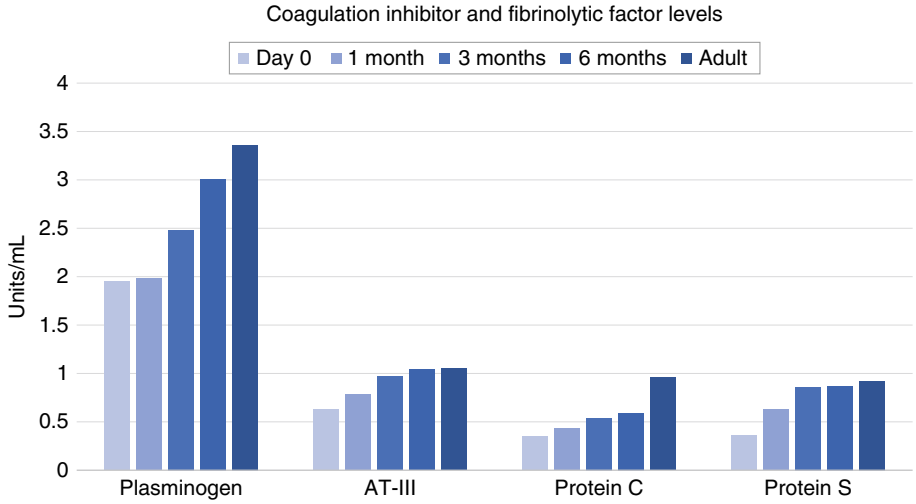


Figure 16.4 NEW Vitamin K-dependent coagulation factors and contact factors in full-term infants through adulthood. AT-III = Antithrombin III. (Source: Adapted from Andrew et al. [5].)

inhibitor type 1 (PAI-1), the major inhibitor of plasminogen activation, is similar in neonates and adults [22]. Due to these imbalances and a qualitatively dysfunctional form of plasminogen, plasmin is generated at much slower rates in neonates [21]. Overall, the balance of factors favors a reduction in fibrinolytic activity.

In spite of these quantitative and qualitative differences in neonatal hemostasis, healthy neonates rarely suffer from spontaneous hemorrhage or thrombosis. This suggests that the maturation of procoagulants and anti-coagulant factors maintain a relative balance in healthy neonates. However, thrombotic complications are more common in neonates, and thromboelastography (TEG) has shown that neonates and infants actually clot faster and have increased clot strength compared with adults [7]. For patients undergoing cardiac surgery, this balance can be easily disrupted and these patients can be placed at risk for both bleeding and thrombotic complications.

KEY POINTS: DEVELOPMENTAL HEMOSTASIS' EFFECT ON COAGULATION

- At birth, many pro- and anti-coagulation factors are quantitatively and quality deficient, but reach adult levels and function by 1 year of age.
- The parallel maturation of coagulation and coagulation inhibitors maintain the delicate balance between thrombosis and bleeding in infants.

Influence of congenital heart disease on coagulation

In addition to the age-related effects on coagulation factor levels and function, children with congenital heart disease (CHD) have complex alternations in their whole blood

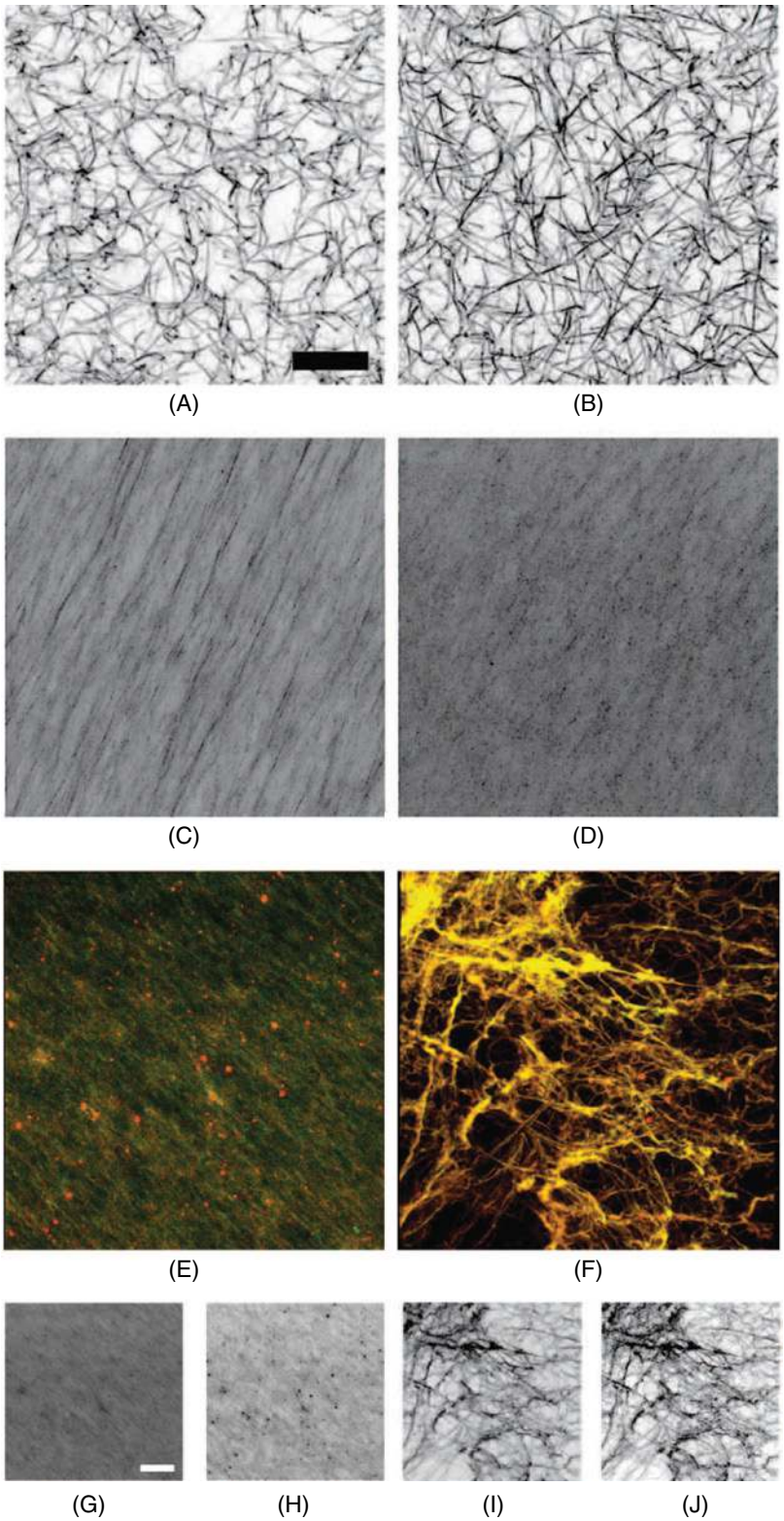


Figure 16.5 Confocal microscopy analysis of clots constructed from both purified neonatal and adult fibrinogen. Clots were formed from purified adult (A, B) or neonatal (C, D) fibrinogen at a concentration of 2.5 (A, C) or 3.5 mg/mL (B, D) fibrinogen in the presence of 10 μg/mL thrombin. Clots were also formed by combining neonatal and adult fibrinogen in a 2.5 : 1 (E, G, H) or 1 : 2.5 (F, I, J) ratio to create clots simulating conditions observed after transfusion with a total fibrinogen concentration of 3.5 mg/mL in the presence of 10 μg/mL thrombin. Neonatal fibrinogen was labeled with Alexa-Flour 488 (green) to allow for separate visualization of adult and neonatal fibrinogen labeled with Alexa-Flour 555 (red). Representative images are presented. For combined fibrinogen samples, overlaid neonatal and adult fibrinogen channels (E, F) and corresponding individual neonatal (G, I) and adult fibrinogen (H, J) channels are presented. Scale bar = 20 μm. (Source: Brown et al. [18]. Reproduced with permission of Wolters Kluwer Health, Inc.)

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composition and coagulation profile, even more so in the presence of long-standing hypoxemia. Since the current practice of pediatric cardiac surgery is to perform corrective procedures in infancy, most of the studies on the effects of long-standing hypoxemia are several decades old. However, children with delayed surgical repair or single ventricle physiology (SVP) who live with chronic hypoxemia will develop cardiac pathophysiology-induced coagulation abnormalities that affect the hematologic, endothelial, and hemostatic systems. These patients are at increased risk for perioperative bleeding and clotting due to the complex interplay of coagulation abnormalities including secondary erythrocytosis, thrombocytopenia, impaired platelet function, deficiency of vWF multimers, and a range of clotting deficiencies.

Erythrocytosis and hemostasis

Irrespective of the primary cardiac lesions, patients with chronic hypoxemia often develop *secondary erythrocytosis*, which refers to an isolated increase in red blood cells (RBCs). This is in contrast to polycythemias that result in a marked increase in all three blood cell lines (RBCs, white blood cells, and platelets). In cyanotic heart disease, long-standing hypoxemia and reduced tissue oxygenation stimulate the kidneys to produce erythropoietin (EPO). This secondary erythrocytosis is an adaptive physiologic mechanism designed to compensate for inadequate oxygenation. However, in the presence of a persistent right-to-left shunt causing chronic hypoxemia, tissue oxygenation cannot improve beyond a certain point. Nevertheless, the kidneys continue to secrete EPO, leading to a further increase in red cell mass and blood viscosity. As blood viscosity increases with the higher number of hematocrits, blood flow may become sluggish and increase the risk of thrombosis and infarction. In fact, the increased mass has been linked with an increased risk of cerebrovascular events in neonates and infants with cyanotic heart disease [23].

In addition to secondary erythrocytosis, many patients with CHD demonstrate abnormal hemostatic profiles. While this is multi-factorial, qualitative and quantitative deficiencies in both platelets and fibrinogen are implicated. Patients with hematocrits above 60–65% often have decreased platelet counts. The thrombocytopenia seen in CHD patients is due to both decreased platelet production and increased peripheral destruction due to platelet activation from the high shear stress generated by increased blood viscosity [24]. Recent studies using TEG suggest that despite normal to elevated fibrinogen concentration, the fibrinogen function may be impaired. Cui and colleagues found that baseline tracings in patients with preoperative hematocrits >54% have decreased peak amplitude on TEG and TEG-functional fibrinogen when compared to normal patients [25]. Similarly, Jensen and colleagues demonstrated that patients with a preoperative hematocrit >57% have a smaller angle (alpha), primarily representative of the fibrinogen contribution to clot formation [26]. In addition, many patients with CHD have reduced levels of vitamin K-dependent factors (II, V, VII, X) likely due to chronic hypoxia and chronic passive congestion of the liver [27]. Finally, these patients appear to have accelerated fibrinolysis based on increased levels of D-dimers and elevated plasminogen activator inhibitor type **1** (PAI-1). However, it is unclear if the accelerated fibrinolysis is due to low-grade intravascular thrombosis, increased fibrinolysis, or increased turnover of fibrinogen [28].

Table 16.2 Coagulation factor levels (mean ± SD) over time for the subgroup of 17 patients who had complete samples drawn at each stage

Variable	Stage I	Pre-BDG	Pre-Fontan	Post-Fontan
Fibrinogen (mg/L)	200.5 ± 70	203.5 ± 86	292.8 ± 76	350.5 ± 93
Antithrombin (%)	36.8 ± 12	75.4 ± 18[a]	93.1 ± 16[b]	56.9 ± 15
Protein C (%)	17.7 ± 9	43.2 ± 12[a]	60.2 ± 16[b]	56.9 ± 15
Protein S (%)	34.1 ± 17	81.3 ± 16[a]	71.1 ± 18	76.3 ± 19
Factor II (%)	37.5 ± 14	64.7 ± 15[a]	77.8 ± 13	81.9 ± 11
Factor V (%)	67.9 ± 19	79.1 ± 15	86.9 ± 21	71.8 ± 19
Factor VII (%)	32.7 ± 14	49.3 ± 13[a]	57.9 ± 15	49.2 ± 14
Factor VIII (%)	50.3 ± 21	63.5 ± 26	90.9 ± 36	175.5 ± 89[c]
Factor IX (%)	32.5 ± 14	47.2 ± 17	62.9 ± 13	72.5 ± 18
Factor X (%)	33.2 ± 9	63.6 ± 15[a]	71.5 ± 13	72.4 ± 16

Data are mean ± SD. BDG, Bidirectional Glenn. The following symbols denote significant changes ($P < 0.005$) between selected stages:
[a] Stage I to pre-BDG;
[b] Pre-BDG to pre-Fontan;
[c] Pre-Fontan to post-Fontan.
Adapted from Odegard and colleagues [29]

While chronic hypoxemia affects multiple aspects of the coagulation system, a prospective longitudinal study of coagulation factors in 20 neonates with hypoplastic left heart syndrome (HLHS) at each stage of their palliation highlighted the complexity of hemostatic changes in congenital cardiac patients. In these children, significantly decreased levels of fibrinogen, vitamin K-dependent factors (II, VII, XI, and X), factors V and VII, as well as anti-coagulation factors (anti-thrombin, Protein C, Protein S, and plasminogen) were noted after initial palliation. These abnormalities persist through the bidirectional cavopulmonary anastomosis and just prior to the Fontan completion. Even after Fontan completion, many of these abnormalities persist, with the exception of an increase in FVIII levels and activity (Table 16.2). It is likely that the imperfect balance of procoagulant and anticoagulant factors contributes to the significant incidence of thrombotic events that occur in these patients [29].

In summary, the hemostatic abnormalities in patients with CHD are complex and include secondary erythrocytosis, thrombocytopenia, impaired fibrinogen function, and multiple coagulation factor deficiencies. Despite our best efforts at minimizing the effects of cardiac surgery on hemostasis, the underlying qualitative and quantitative hemostatic changes related to CHD itself predispose these patients to both bleeding and thrombosis.

KEY POINTS: INFLUENCE OF CONGENITAL CARDIAC PATHOPHYSIOLOGY ON COAGULATION

- Children with CHD have complex alterations in their coagulation profile due to long-standing hypoxemia and liver congestion.

- Children with chronic hypoxemia develop secondary erythrocytosis which results in elevated hematocrit levels, decreased platelet count and function, and impaired fibrinogen function.
- Coagulation abnormalities persist in children with single-ventricle anatomy and physiology through all stages of palliation.

Preoperative considerations

Predictors of bleeding post-CPB

Bleeding in the perioperative period of cardiac surgery is associated with increased incidence of postoperative complications and mortality, both from the direct effects of bleeding and from the therapies deployed to restore hemostasis. As an example, blood transfusion has been shown to be associated with a dose-dependent increased risk of postoperative infection and mortality in pediatric surgical patients [30]. Several studies have suggested that the increased bleeding risk observed in patients with CHD may be attributable to multiple contributing factors including both quantitative and qualitative differences in coagulation factors, relative immaturity of the coagulation system, endothelial dysfunction, intrinsic risk of surgical procedures, associated comorbidities (e.g., liver dysfunction), and iatrogenic factors (e.g., anticoagulation therapies, central venous access) [26, 31, 32]. Among children with CHD undergoing surgery, those with cyanotic heart disease (e.g., single ventricle physiology) are considered at higher risk for both intraoperative bleeding and postoperative thrombotic complications [29, 33]. Although the exact mechanisms for bleeding and thrombotic risks in children with CHD remain poorly understood, a complex multifactorial etiology including modifiable and non-modifiable factors is hypothesized.

Figure 16.6 summarizes the risk factors reported in the literature and that are discussed throughout this chapter. Patient-risk factors are mainly related to the age of the patient at the time of surgery. Several authors have reported a strong association between age and the incidence of bleeding, with the highest risk of hemorrhage being reported in neonates [35, 36]. Age at the time of surgery is also associated with surgery-specific risk factors as neonates often require complex surgical procedures involving prolonged CPB duration sometimes associated with deep hypothermic cardiac arrest (DHCA) [37]. Another surgery-related risk factor is the timing for surgery (i.e., need for urgent or emergent surgery) which often mean hemodynamic instability (i.e., heart failure sometimes requiring extracorporeal membrane oxygenation [ECMO]), high requirement of ventilatory or inotropic support, and presence of multiple organ failure (i.e., acute kidney injury, liver failure, pulmonary edema). As discussed above, different bleeding risks have been reported according to the type of CHD. The presence of cyanosis will have an impact on coagulopathy, fibrinogen polymerization, and platelet function [26, 38]. Patients with cyanotic heart disease often require multiple surgical procedures, also increasing the bleeding risk.

Although several authors have studied the predictive values of preoperative coagulation testing (i.e., standard laboratory tests, viscoelastic tests, thrombin generation, or platelet function), none of these tests have been shown to accurately predict perioperative bleeding, a testimony to the complexity and the multifactorial nature of perioperative bleeding [39, 40].

Although most risk factors are non-modifiable, it is important to estimate the risk before surgery in order to choose the appropriate tools to monitor and treat coagulopathy using a

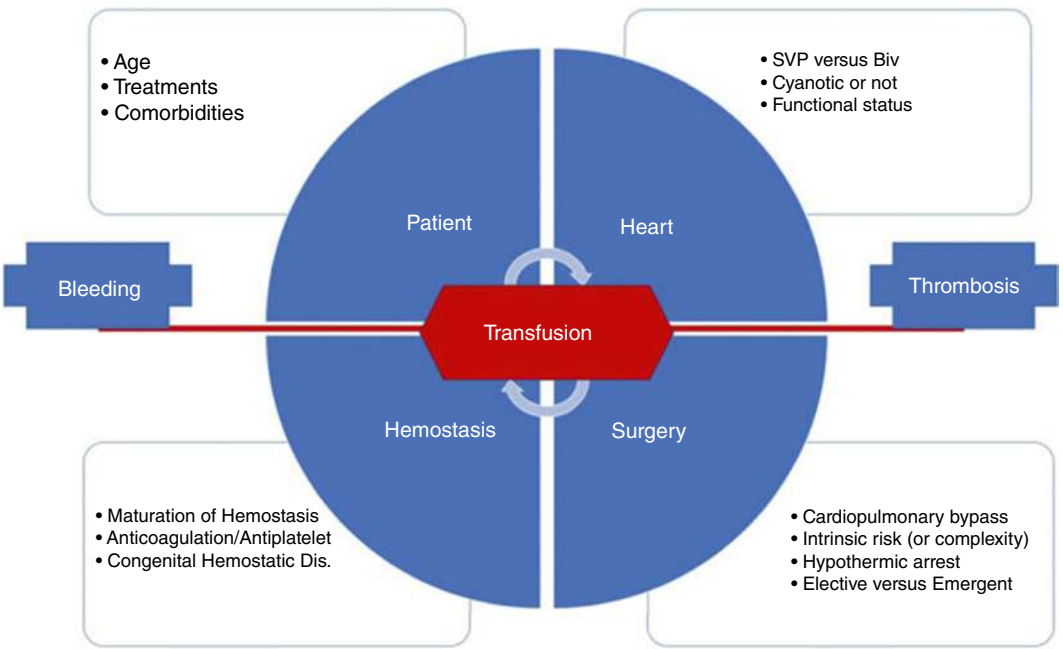


Figure 16.6 Factors affecting perioperative hemostasis in pediatric cardiac surgical patients. (Source: Cohen et al. [34]. Reproduced with permission of Cambridge University Press.)

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standardized and targeted transfusion algorithm that we will discuss later in this chapter.

KEY POINTS: PREDICTORS OF BLEEDING POST-CPB

- Bleeding in the perioperative period of cardiac surgery is associated with an increased incidence of postoperative complications and mortality.
- Although the exact mechanisms for bleeding and thrombotic risks in children with CHD remain poorly understood, a complex multifactorial etiology including modifiable and non-modifiable factors is hypothesized.
- Preoperative coagulation tests have not been shown to accurately predict perioperative bleeding.

Preoperative laboratory testing

During the preoperative evaluation of patients coming for cardiac surgery, practitioners should perform a complete history and physical examination to determine what laboratory testing is necessary. Patients with cyanotic heart disease may have secondary erythrocytosis, thrombocytopenia, abnormal levels of fibrinogen, and other coagulation factors. In addition, these children often have abnormal liver function tests secondary to systemic hypoperfusion, heart failure, hypoxemia, and hyperviscosity. Because the detection of these abnormalities and correction may help minimize the risk of bleeding during the intraoperative period, it is recommended that a basic electrolyte panel, complete blood cell count with differential, coagulation profile, a type and crossmatch, and liver function tests be obtained [41]. Practitioners should also question the patient and family members about bleeding or thrombotic events to determine if further hematology work up is necessary.

For outpatients with acyanotic heart disease, several institutions have adopted strategies aimed at minimizing preoperative laboratory testing to reduce patient stress related to blood draws, minimize the risk of iatrogenic anemia, and reduce additional costs. In a survey of 12 congenital cardiac surgical programs, 11 institutions still send most baseline laboratory testing. However, many practitioners reported that in the year following the original survey, no cases were canceled or their management changed because of these laboratory results. While most practitioners agreed that a type and screen and complete blood count would be sufficient to manage outpatients, only one institution has implemented these changes thus far [42].

KEY POINTS: PREOPERATIVE LABORATORY TESTING

- A complete blood count, a basic electrolyte panel with liver function tests, coagulation profile and a type and cross are recommended for most patients presenting for cardiac surgery.
- A thorough history and physical examination will determine if additional laboratory testing is necessary to screen for potential bleeding or thrombosis risks.

Preoperative anemia

One of the cornerstones of modern Patient Blood Management protocols is the identification and the treatment of preoperative iron deficiency with or without anemia. Pediatric cardiac surgical patients can range from newborns to adolescents, suffering from cyanotic or non-cyanotic cardiac defects, which result in varying baseline hemoglobin (Hb) concentrations and ferritin levels. The optimal preoperative Hb values for pediatric cardiac surgery remain to be determined as the World Health Organization (WHO) definition of anemia for pediatric patients does not apply to neonates and children with variable degrees of cyanosis and secondary erythrocytosis. However, one could argue that any pediatric cardiac surgical patient with a preoperative Hb below 11 g/dL should be considered anemic and might be suitable for preoperative anemia study and therapy. Higher thresholds might be worth consideration, especially in children with cyanotic heart defects. If a Hb of 11 g/dL is chosen as a threshold for intervention, up to 50% of patients with CHD would be diagnosed with preoperative anemia and should therefore be started on iron therapy before their procedure. In neonates and children undergoing noncardiac surgery, preoperative anemia was associated with an increased risk of mortality and postoperative complications [43, 44]. In cardiac patients, preoperative anemia was associated with an increased risk of perioperative acute kidney injury (AKI) in a retrospective cohort study of 220 patients undergoing cardiac surgery [45]. In addition, preoperative anemia has been shown to increase the risk of allogeneic transfusion in children undergoing noncomplex cardiac surgery (i.e., repair of ventricular or atrioventricular septal defects) [46]. Therefore, similar to adult patients, assessment of preoperative anemia and appropriate treatment should be recommended to avoid complications associated with perioperative and reduce the need for avoidable allogeneic blood transfusions.

Iron deficiency is present in an estimated 70–80% of pediatric patients with inflammatory bowel disease and has been shown to impair health-related quality of life [47]. Iron deficiency is also common in patients with chronic kidney disease and renal failure and is associated with increased all-cause and cardiovascular mortality [48]. Iron deficiency was recently studied in children with heart failure [49]. In this cohort, the authors found that 56% of children with heart failure presented with iron deficiency. They also found that iron deficiency was associated with greater risks of ventricular assist device implantation, heart transplantation, or death. In adults, iron deficiency has been repeatedly shown to be associated with greater cardiovascular and all-cause mortality, poorer functional capacity, lower health-related quality of life, and greater readmission rates in patients with chronic heart failure. Multiple randomized controlled trials have shown that treating iron deficiency with intravenous iron improves each of these outcome measures [50, 51].

Keeping that in mind, preoperative treatment of iron deficiency anemia is recommended in some adult and pediatric guidelines for the management of heart failure [52] or blood conservation in adults and pediatric cardiac surgical populations [53, 54]. In children undergoing cardiac surgery, the optimal approach for preoperative treatment of iron deficiency anemia has never been appropriately studied. For the preoperative administration of iron, only a very limited number of studies exist, most of them looking at oral iron

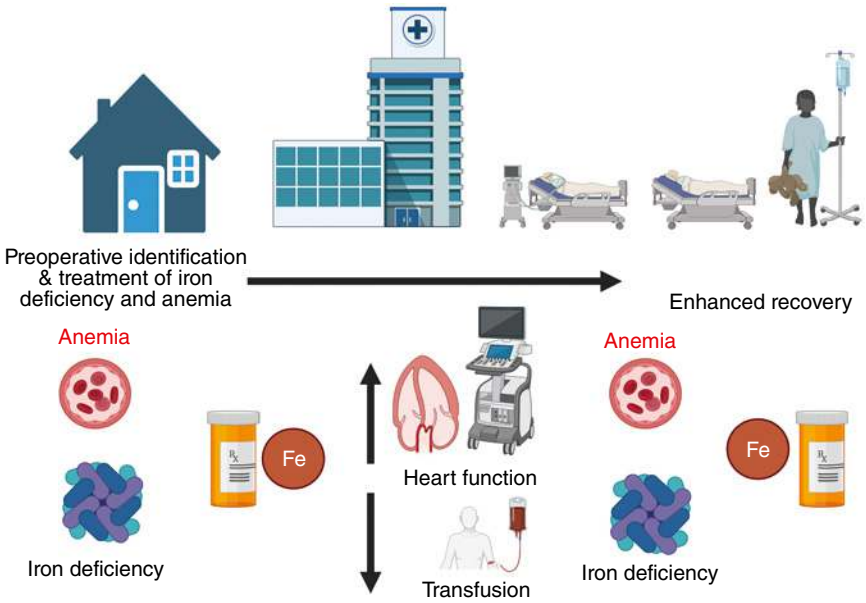


Figure 16.7 Integration of iron deficiency and anemia management into guidelines for enhanced recovery following pediatric cardiac surgery. (Source: made in ©BioRender - biorender.com.)

supplementation [55]. The largest study using intravenous iron has been published by Hassan and colleagues in 2017 in which the authors demonstrated that Ferumoxytol was effective in treating iron-deficiency anemia in a small retrospective cohort of 54 patients [56]. The members of this group pointed out that a slow infusion rate and close monitoring allowed early detection of the infrequent adverse drug reactions. Although the concomitant administration of EPO has sometimes been suggested, data supporting the efficacy and safety of EPO in pediatric cardiac patients is sparse. In a small retrospective study, Shimpo and colleagues demonstrated that the administration of up to 300 IU/kg EPO was effective as an adjuvant therapy for open-heart surgery [57]. However, the appropriate dosing regime has not been determined thoroughly. Appropriately designed studies are urgently needed to define the optimal treatment strategy (oral vs. intravenous iron), the dose, the duration, and to understand whether the addition of EPO would sometimes be beneficial.

Although one of the challenges often reported for preoperative assessment and treatment of anemia in adult cardiac surgical patients is the short window between the initial patient assessment and the time of surgery, this is often not an issue in infants and children who usually have to wait weeks, sometimes months, before their surgical procedure. We should therefore take advantage of the wait time to correct iron deficiency and anemia. In addition, postoperative iron deficiency and hospital-acquired anemia are also important issues that require our attention, and efforts should be undertaken to reduce unnecessary blood sampling and treatment of iron deficiency anemia should be initiated or resumed in the postoperative period before hospital discharge. The development of enhanced recovery after surgery (ERAS) protocols, as recently emphasized by the members of the American Association of Thoracic Surgeons' Cardiac Clinical Practice Standards Committee [58], is an excellent opportunity to integrate perioperative management of iron deficiency and anemia integrated into the multimodal protocol to optimize enhanced recovery following pediatric cardiac surgery (Figure 16.7).

KEY POINTS: PREOPERATIVE ANEMIA

- Preoperative anemia and iron deficiency are prevalent in the pediatric cardiac surgical population.
- Anemia and iron deficiency should be evaluated and treated preoperatively.
- The optimal therapeutic strategy (e.g., oral vs. intravenous iron, with or without EPO) remains to be determined.

Autologous donation

Preoperative autologous donation (PAD) refers to the collection and anticoagulation of whole blood from a patient for anticipated perioperative transfusion. The amount of blood collected from a single donation is limited to about 10% of the patient's total blood volume. While it may eliminate the risk of blood-borne infections and may diminish immune modulation, PAD remains controversial due to issues with safety, cost, logistics around surgical scheduling, and the potential pathophysiologic effects on a child with complex CHD. Therefore, this practice is generally reserved for relatively healthy adolescent patients with simple cardiac anomalies.

In contrast, autologous intraoperative blood collection and retransfusion have become more popular in order to minimize the risks associated with PAD. Acute normovolemic hemodilution (ANH) is the removal of whole blood from the patient before CPB while maintaining normovolemia through the infusion of crystalloids or colloids and then transfusing the blood after CPB. Patient selection depends on baseline hematocrit and hemodynamic stability,

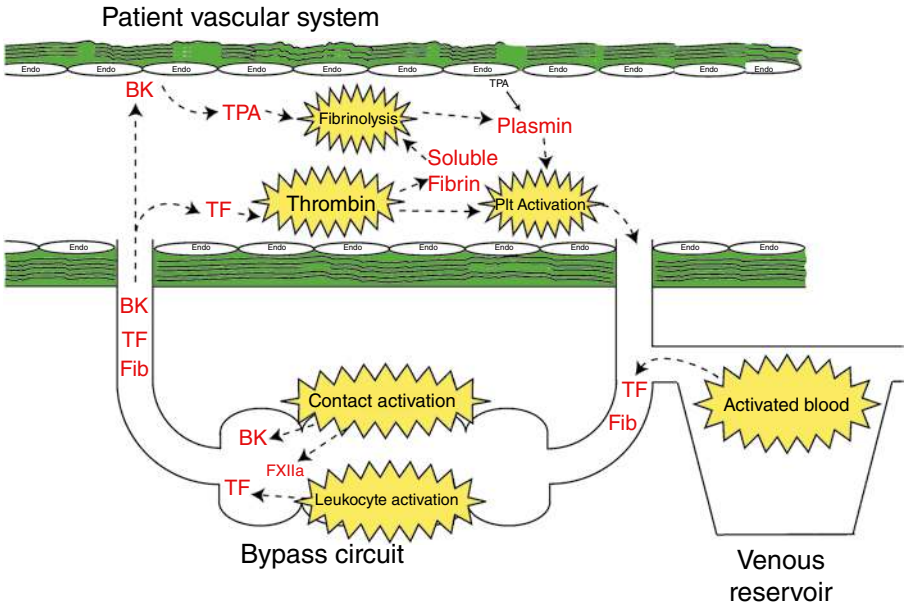


Figure 16.8 Summary of hemostatic activation mechanisms on cardiopulmonary bypass. BK = bradykinin; FXIIa = activated factor XII; TF = tissue factor; TPA = tissue plasminogen activator; Plt = platelets; Fib = fibrin degradation products; Endo = endothelium. (Source: Sniecinski et al. [62]. Reproduced with permission of Wolters Kluwer Health, Inc.)

the composition of the CPB prime, and the targeted hematocrit on CPB. A retrospective study of 209 pediatric patients undergoing cardiac surgery (with ANH when appropriate), showed that 59.6% of patients >6 kg did not receive any blood transfusions, while all patients under 6 kg received a blood transfusion. Another study of 36 patients <10 kg matched 1:1 for intraoperative autologous blood collection and retransfusion vs. standard practice, demonstrated that patients in the study group received fewer blood products overall (47 mL/kg vs. 68 mL/kg) without increased 24 hours chest tube output, mechanical ventilation, or intensive care units (ICU) length of stay. Of note, platelet count and fibrinogen levels were significantly lower in the study group compared to the control group. While these studies show that the practice is relatively safe, this practice does not necessarily reduce overall blood transfusions in patients under 18 kg [59–61].

KEY POINTS: AUTOLOGOUS DONATION

- PAD is the collection and anticoagulation of whole blood from a patient for anticipated perioperative transfusion.
- While PAD has fallen out of favor, intraoperative autologous blood collection and re-transfusion may reduce blood transfusions in patients >6 kg without increased risks.

CPB-associated coagulation changes

Exposure to CPB circuit

Cardiopulmonary bypass (CPB) is a unique scenario when the patient's blood is exposed to non-endothelial/non-physiologic surfaces leading to a widespread activation of the coagulation, fibrinolytic, and inflammatory systems (Figure 16.8).

Several mechanisms are involved in the hemostatic activation induced by CPB [62, 63]. The contact system (bradykinin system) is activated immediately when blood is in contact with the CPB artificial surfaces. In addition, factor XII autocleaves itself upon contact with a variety of anionic surfaces leading to activated FXII, which converts prekallikrein into active kallikrein. Plasma kallikrein creates a positive feedback loop by producing more activated FXII, as well as producing bradykinin from high-molecular-weight kininogen (HMWK) [64]. Bradykinin levels increase 10-fold due to increased HMWK cleavage as well as reduced lung clearance secondary to minimal pulmonary blood flow [65]. This has important implications for fibrinolysis because elevated bradykinin levels induce secretion of tPA. The role of thrombin generation during CPB is well-documented, even in the presence of adequate anticoagulation [66]. The activation of the contact system, as well as the exposure of TF on the membrane of traumatized cells by aspiration of the surgical field and CPB, expression of TF due to inflammation and due to the generated thrombin will promote a vicious circle of activation of the hemostatic and fibrinolytic system. Endothelial cells release tissue-type plasminogen activator (tPA), a major activator of plasminogen leading into fibrin-degrading plasmin. In the setting of CPB, soluble and circuit-bound fibrin provides a huge surface for plasminogen activation to occur. There is a 10- to 100-fold increase in plasmin generation shortly after the commencement of CPB, and plasmin generation, along with fibrin degradation, remains increased 10- to 20-fold throughout the duration of CPB [67]. During CPB, fibrin formation and degradation rates are nearly equal, indicating that much of the fibrin degradation is not at the sites of vascular injury. This hyperfibrinolytic state consumes fibrinogen, leaving less

available for coagulation postoperatively. After CPB, platelet adhesion is decreased to the destruction of GPIb receptors by plasmin and by the shear stress. In addition, platelet aggregation is also decreased by thrombin, plasmin, and fibrin degradation products. Altogether, these processes lead to a quantitative and qualitative consumption of coagulation factors and platelets during CPB.

Because coagulation and immune systems are associated, inflammation has multiple mediators that can create profound amplification in coagulopathy. A sepsis-like clinical picture, named systemic inflammatory response syndrome (SIRS), often results from CPB and can be linked to the close relationship between inflammation and coagulation. Leukocytes, including neutrophils and monocytes, bind to and are activated by the surface of the CPB, which leads to an increase in tissue expression, procoagulant activation, and thrombin generation. The generation of inflammatory cytokines leads to increased vascular permeability, neutrophil infiltration into the tissue, and production of acute-phase proteins.

In addition, CPB needs to be primed with blood, fluid, or a combination leading to a variable degree of hemodilution promoting even more than coagulopathy.

Hemodilution and CPB prime

Postoperative hemostasis is greatly influenced by the degree of hemodilution that occurs as a result of CPB. The effect of dilution depends on the patient's blood volume, the baseline blood concentrations (hematocrit, coagulation factors, platelets), and the volume and components of the CPB circuit prime. In children, hemodilution is an independent predictor of increased transfusions. As a result, smaller circuits have become more popular in order to minimize hemodilution, reduce the inflammatory response induced by CPB components, and decrease overall blood transfusions. Miniaturizing the CPB circuit is achieved by the elimination of non-essential components, using small-volume circuit components (oxygenator, filters, cannulae), decreasing the length and diameter of circuit tubing, using a remote pump head, assisted venous drainage, retrograde autologous circuit priming, and microplegia techniques [68]. As a result, some institutions report prime volumes of 95–110 mL for infants <5 kg. However, efforts to reduce the prime volumes require careful planning and meticulous management of bypass to mitigate risks.

Dilutional anemia

Originally, hemodilution during hypothermic CPB was used to reduce the use of blood products, promote microcirculatory flow and improve tissue perfusion. However, concerns emerged about postoperative cognitive impairment from reduced perfusion pressure, decreased oxygen-carrying capacity, and increased cerebral blood flow causing an increased risk for cerebral microemboli. Subsequent studies have demonstrated that for infants undergoing biventricular repair, a hematocrit ~ 24% or higher at the onset of low-flow CPB is associated with higher Psychomotor Development index scores at 1 year, reduced lactate levels, and improved fluid balance [69]. Some studies suggest that lower hematocrit levels are safe if mixed venous oxygen saturation, near-infrared spectroscopy cerebral oxygen saturation, and lactate levels are maintained within the normal range [70]. Unfortunately, most of the studies evaluating lower hematocrits on CPB contain a small heterogeneous population and the nadir hematocrit was ~22%. In summary, due to differences in diagnosis, age at operation, and CPB management, it is unlikely that hematocrit alone can indicate when the benefits of RBC transfusion outweigh the risks of hemodilution.

Dilution of coagulation factors

In addition to dilutional anemia, many coagulation factors have been noted to decrease at the initiation of CPB. Brown and colleagues demonstrated a decrease in both fibrinogen and FXIII due to hemodilution, which were restored to baseline levels after the transfusion of cryoprecipitate [18]. Of particular importance, the hemodilutional effects of CPB in neonates and infants often result in low fibrinogen levels that lead to impaired fibrin formation, inadequate clot formation, and increased risk of post-CPB bleeding [18, 71–73] (Figure 16.9).

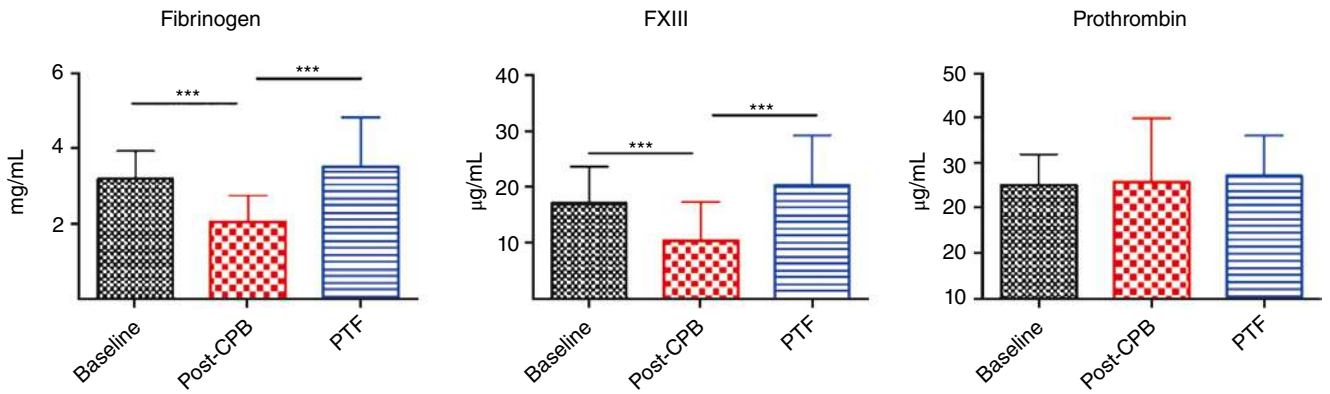


Figure 16.9 Effects of hemodilution on coagulation factors in neonates undergoing cardiopulmonary bypass. Post-CPB = cardiopulmonary bypass, F = Factor; PTF = Post Transfusion. (Source: Brown et al. [18]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Composition of CPB prime

In addition to miniaturizing the circuit volumes for pediatric patients, the prime composition is often adapted to the particular requirements of the patient and the operation. That being said, the majority of institutions still use a blood prime for infants and neonates. The lower the blood volume and hematocrit of the patient, the more banked blood needs to be added into the prime. While several institutions have access to fresh whole blood (<48 hours after donation), the majority of institutions use reconstituted whole blood (fresh frozen plasma (FFP) plus RBCs). Advocates for fresh whole blood prime believe that it reduces coagulopathy and also CPB-mediated inflammation. However, Mou and colleagues performed a randomized trial in children <1 year of age comparing fresh whole blood with reconstituted blood. The authors found that patients who received fresh whole blood had increased ICU length of stay and more fluid overload [74]. In contrast, several other studies have demonstrated that patients receiving whole blood received fewer transfusions, significantly less chest tube output, and shorter length of mechanical ventilation and ICU stays [75–77]. Furthermore, adequately powered studies performed in the context of the current multimodal strategy to manage coagulopathy are required before the safety and efficacy of fresh whole blood can be determined.

While most institutions still use RBCs and FFP in the CPB prime for neonates, there is little high-grade evidence to support its use in older patient populations. Some institutions use albumin to maintain oncotic pressure and reduce fluid accumulation, while proponents of FFP argue that in addition to maintaining oncotic pressure, FFP increases the level of coagulation factors and reduces intraoperative transfusion requirements in complex neonatal and cyanotic patients. In a study of 60 patients weighing 7–15 kg randomized to FFP or crystalloid prime, Dieu and colleagues did not report any significant differences in median postoperative blood loss or transfusion requirements [78]. Other studies have demonstrated that patients with FFP prime have higher fibrinogen concentrations and improved TEG values at the end of CPB, but this was not associated with a decrease in postoperative transfusions. Unfortunately, the composition of the prime is often a matter of opinion and institutional practice and differs widely across institutions. The only consensus regarding CPB prime is minimizing transfusion requirements and hemodilution. Additional pediatric-specific trials are needed to determine the optimal CPB prime composition.

KEY POINTS: HEMODILUTION AND CPB PRIME

- Significant hemodilution of hematocrit and coagulation factors due to the CPB circuit contributes to post-bypass coagulopathy in patients undergoing congenital cardiac surgery.
- The degree of hemodilution depends on the patient's blood volume, baseline hematocrit, and the volume of the CPB circuit and its components.
- Due to significant hemodilution in neonates, many institutions still use either whole blood or reconstituted blood (FFP and RBCs) in their circuit prime.

Anticoagulation

Anticoagulation during CPB is necessary to prevent thrombin formation and subsequent clotting as blood comes into contact with the non-endothelial CPB surfaces. Unfractionated heparin is the primary anticoagulant used to inhibit not only the formation of thrombin but also the activity of circulating thrombin through its binding to AT [79]. Unfractionated heparin is usually administered at the dose of 300–400 IU/kg. The administration of 400 U/kg of heparin has been shown to produce adequate prolongation of activated clotting times (ACT) >480 s. However, a word of caution is required for neonates where standard weight-based doses have been shown to inadequately suppress thrombin generation and activity. Consequently, some centers have adopted patient-specific heparin concentration-based heparin management protocols in infants aged <6 to 12 months [80–82]. Individualized heparin doses based on heparin dose-response analysis have been used in some studies [83]. However, in a recent large cohort of children who received unfractionated heparin for CPB, Nakamura and colleagues found that heparin responsiveness before CPB was not reliably predicted by either *in vitro* heparin dose-response slopes estimated by the HMS Plus System (Medtronic, Minneapolis, MN) or regression models using commonly available preoperative clinical and laboratory data [84]. The strength of the correlation between predicted and observed heparin responsiveness was found to be at best moderate for young children <5 years. Different techniques have been used to monitor anticoagulation intraoperatively. Standard whole blood clotting time is still routinely used to monitor anticoagulation in children undergoing cardiac surgery. However, some centers have recommended monitoring heparin concentration along with the ACT as a more accurate guide for the administration of heparin to infants during CPB [85].

Despite the use of anticoagulation monitoring, anticoagulation using unfractionated heparin remains challenging in neonates and infants. Differences between commercialized heparin manufacturers and others have also been reported, which highlights the need for appropriate monitoring of anticoagulation.

Another reason for the difference in heparin sensitivity in the pediatric population may be related to the anticoagulation activity of AT, which can be influenced by age, heart failure, liver dysfunction, and inflammation. In a study by Manlhiot and colleagues, low circulating AT activity was associated with lower heparin efficacy, which ultimately leads to a decreased ability to suppress thrombin generation during CPB [86]. Determination of risk factors for heparin resistance, and potentially, AT supplementation, may individualize and improve anticoagulation treatment. In the presence of AT deficiency, FFP is usually administered because of its frequent availability in the operating room. Even though AT concentrate has sometimes been used in children supported with ECMO, there is a paucity of studies assessing the efficacy and safety of AT supplementation in neonates and children undergoing cardiac surgery. In a small cohort of infants and children with an inadequate response to heparin, Lopez and colleagues reported that 50 ± 6 U/kg of AT was effective in achieving adequate anticoagulation [87]. AT levels are sometimes included as part of the

preoperative laboratory testing. Because of the low prevalence of congenital AT deficiency, routine measurement of AT levels is not recommended. However, preoperative measurement of AT level should be considered in the presence of risk factors (e.g., neonates exposed to preoperative heparin infusion).

After a patient is weaned off CPB, protamine is administered to neutralize the effect of heparin. The protamine dose is usually based on the total amount of heparin administered during CPB. However, both residual heparin and protamine overdose are associated with increased postoperative bleeding. Most centers use a protamine-to-heparin ratio of 1:1. Based on the pharmacokinetic of heparin, a 1:1 ratio could lead to protamine overdose and bleeding; it is often recommended to use a protamine-to-heparin ratio of 1:2 ratio. Protamine dose can also be estimated based on heparin concentration monitoring [81, 83].

KEY POINTS: ANTICOAGULATION

- ACT is a whole blood test, and the clotting time obtained from an ACT is not specific to anticoagulation and any prolongation could be explained by the underlying coagulopathy.
- The baseline ACT, although routine in most cardiac programs, is of little value as it has never been shown to predict heparin resistance.
- After protamine, ACT returning to the baseline value does not make sense due to the non-specificity of ACT. The ideal method to assess the presence of residual heparin is through the use of heparinase tests and the ratio between clotting time with and without heparinase. This could be achieved using ACT or viscoelastic tests [88]. It is usually accepted that a difference of >10% between clotting times with and without heparinase is subjective of residual heparinization.
- The optimal protamine-to-heparin ratio remains to be determined, but 1:1 increases the risk of overdosage and bleeding.

Heparin-induced thrombocytopenia and alternatives to heparin

Prolonged administration of heparin can lead to heparin-induced thrombocytopenia (HIT). HIT is an immune-mediated syndrome manifesting as a drop in platelet count to >50% and life-threatening vascular thromboses (incidence: 30–75%) and can even be associated with mortality in 20–30% of cases. HIT has been reported in adults undergoing cardiac surgery, as well as in children and neonates. Figure 16.10 summarizes the

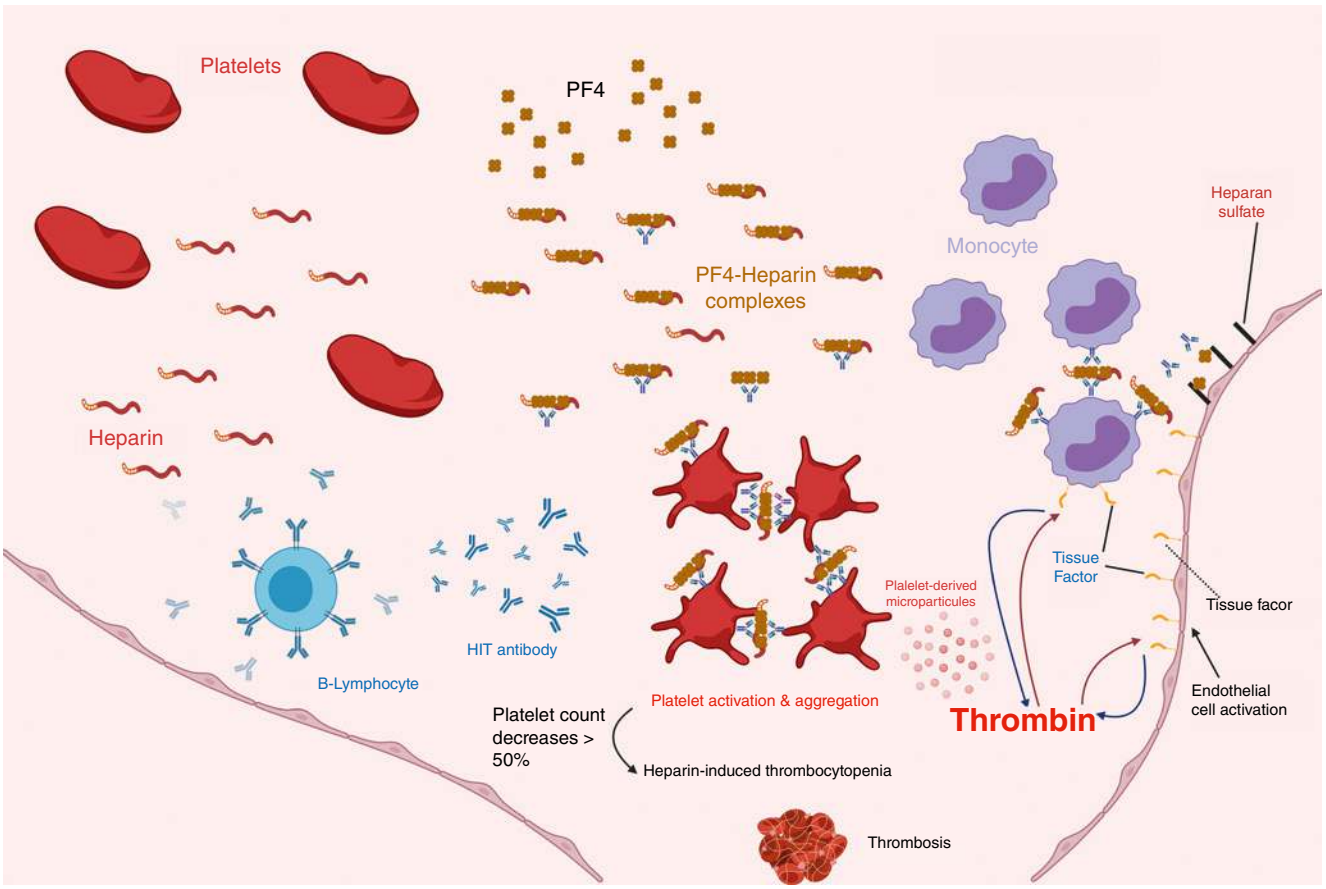


Figure 16.10 Heparin-induced thrombocytopenia. (Source: made in ©BioRender - biorender.com.)

pathogenesis of HIT. The central concept if the formation of heparin-dependent IgG that activates platelets after binding to multimolecular complexes of heparin and platelet factor 4 (PF4) leading to a self-perpetuating cycle of platelet activation, thrombin generation, and further release of PF4 from platelet granules. Endothelial cells and monocytes are also activated by the antiheparin/PF4 IgG resulting in the expression of circulant TF further promoting thrombin generation. The diagnosis of HIT relies on a combination of clinical signs and laboratory criteria. Clinical criteria include thrombocytopenia with a ≥50% platelet count drop or a platelet count decreases <150,000/mm^3, with or without venous or arterial thromboses. Laboratory criteria include the detection of antibodies to heparin/PF4 complexes and positive functional tests of platelet activation or aggregation.

In the pediatric population, the incidence of HIT is around 2–3% of patients receiving heparin anticoagulation. The main risk factor in the pediatric population is the use of intravascular catheters and heparin flushes in neonates and infants.

Three scenarios have been described for HIT. The "typical" onset HIT is seen in about two-thirds of cases and presents about 5 to 10 days after the initiation of heparin administration. The "rapid" onset HIT is seen in about 30% of the cases when HIT develops within hours or the first day of heparin administration. The pathophysiology of the "rapid" onset HIT is thought to be explained by the presence of preexisting heparin/PF4 antibodies due to previous exposure to heparin within 100 days. Finally, "delayed" onset HIT is rare but presents up to 3 weeks after discontinuation of heparin. The pathophysiology is explained by the presence of persistent antibodies that can activate platelets without the presence of heparin.

When HIT is suspected, the assessment begins with the calculation of the pretest probability using the "four Ts": thrombocytopenia, the timing of platelet drop, thrombosis, and other causes of thrombocytopenia (Table 16.3) [89]. In the pediatric cardiac surgical population, the number of etiologies for thrombocytopenia are numerous. It is therefore important to dissociate HIT with other causes of thrombocytopenia. Based on the scoring system in Table 16.3, the decision to proceed with only antigen testing (score 6–8), a positive antigen and functional assays (score 4–5), no laboratory testing when the probability of HIT is low (score 0–3). Antigen assays are used to detect the presence of IgG antibodies to heparin/PF4 complexes, as well as IgA and IgM. Although IgA and IgM can be detected, it seems unlikely that HIT can be developed without the presence of IgG which explains the discrepancy between the presence of detectable heparin/PF4 antibodies in adults treated with heparin (±50%) but only 1–5% develop HIT. Functional tests detect the ability of the heparin/PF4-IgG complex to activate platelets and cause thrombosis. Functional assays are time-consuming, require donor platelets, and are performed only in reference laboratories.

The treatment of clinically suspect HIT requires the interruption of any exposure to heparins, which not only includes unfractionated heparin but also LMWH and heparin-coated materials. The administration of non-heparin anticoagulants is recommended, like direct thrombin inhibitors (bivalirudin or argatroban) or direct Xa inhibitors (fondaparinux).

In contrast to heparins that require antithrombin (AT) to inhibit thrombin, argatroban and bivalirudin are direct thrombin inhibitors (DTIs) that bind to thrombin independent of antithrombin. DTIs, unlike unfractionated heparin (UFH), inhibit both plasma and fibrin-bound thrombin (Figure 16.11). Fibrin-bound thrombin activates platelets in the forming thrombus for clot stabilization. DTIs inhibit clot-bound thrombin, decrease clot stabilization, and promote thrombolysis.

In addition, recent data indicate that argatroban and bivalirudin increase the fibrin network permeability, rendering it less resistant to fibrinolysis. However, in conjunction with the lack of a reversal agent, these effects may contribute to potentially severe bleeding complications within the context of high-dose administration as used during cardiac surgery. There are limited data with regard to the use of argatroban during cardiac surgery, particularly during CPB. Bivalirudin has been studied in a few randomized controlled trials in adults undergoing cardiac surgery. Argatroban and bivalirudin are important anticoagulation alternatives for patients with HIT who require urgent surgery and/or perioperative anticoagulation. Although both argatroban and bivalirudin being employed for more than a decade in the complex setting of cardiac surgery, scientific data are limited to a restricted number of smaller prospective and retrospective, mostly single-center studies, and rarely involving pediatric patients. The unique pharmacokinetics of bivalirudin makes this agent an interesting option, particularly for a short-term, high-dose anticoagulant effect, as needed during cardiac surgery. However, limitations are the lack of a standardized

Table 16.3 Estimating the Pretest Probability of Heparin-Induced Thrombocytopenia: the "four Ts"

	2	1	0
Thrombocytopenia	>50% platelet fall (nadir ≥ 20,000/mm^3)	30–50% platelet fall (or >50% fall due to surgery) or nadir 10–19,000/mm^3	<30% platelet fall or nadir <10,000/mm^3
Timing of platelet count fall or thrombosis	Clear onset between days 5 and 10 or ≤1 day (if heparin exposure within the past 30 days)	Consistent with day 5–10 fall, but not clear (e.g., missing platelet count) or ≤1 day (heparin exposure within the past 31–100 days) or platelet fall after day 10	Platelet count fall ≤4 days without recent preceding heparin exposure
Thrombosis or other sequelae (e.g., skin lesion)	New thrombosis, skin necrosis, post heparin bolus acute systemic reaction	Progressive recurrent thrombosis, erythematous skin lesions, suspected thrombosis not yet proven	None
Other causes of thrombocytopenia not evident	No explanation (besides HIT) for platelet count is evident	Other possible cause is evident	Definite, other cause present

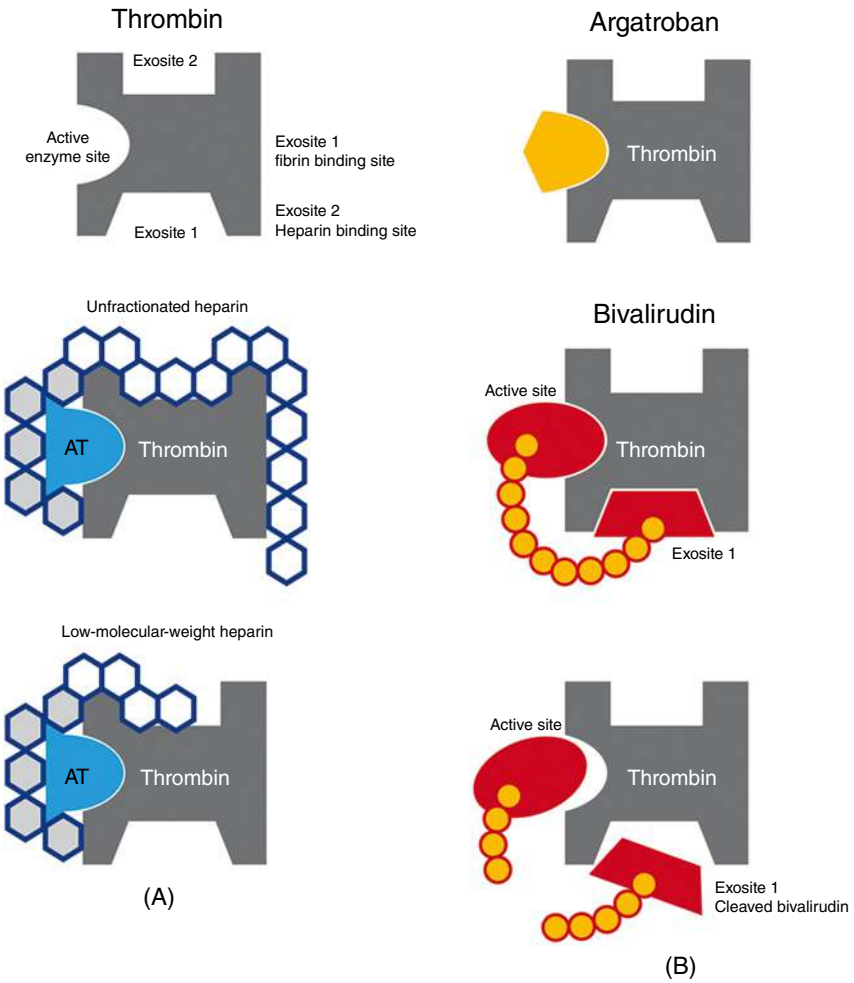


Figure 16.11 Mechanism of action of argatroban and bivalirudin. (A) Indirect inhibition of thrombin by antithrombin, which is activated via unfractionated or low molecular weight heparin. (B) Direct inhibition of thrombin by argatroban and bivalirudin. Bivalirudin is cleaved by thrombin via proteolysis. This represents the major elimination mechanism of bivalirudin. AT = antithrombin. (Source: Koster et al. [90]. Reproduced with permission of Wolters Kluwer Health, Inc.)

reliable point-of-care monitoring during CPB, as well as a reversal agent. The use of bivalirudin was recently studied in a small randomized controlled trial and compared to heparin in children with non-cyanotic heart disease undergoing cardiac surgery [91]. In the absence of a recommended safe dose for children, the adult dose regimen of 1 mg/kg followed by 2.5 mg/kg/hour infusion was used for all children, although 54% of children required an escalation in the dose to maintain an ACT of >480 seconds. The dose required to maintain ACT >480 seconds was 1.7 ± 0.2 mg/kg followed by 3.0 ± 0.7 mg/kg/hour infusion. Bivalirudin did not increase postoperative bleeding and transfusion requirement. In a recent research report, Wolstencroft and colleagues suggested that bivalirudin infusion in children should be started after a loading dose at rates greater than those used in adults [92]. Dose in neonates remains undefined because neither pharmacokinetics nor coagulation pharmacodynamics has been adequately characterized. An infusion rate of 4.5 mg/kg/hour in a 10 kg infant, 4 mg/kg/hour in a 20 kg child, and 3.5 mg/kg/hour in a 30–40 kg child will target an activated clotting time slower than 400 seconds. Adult regimens could be used in those children heavier than 50 kg. In a review article published in 2019, Zaleski and colleagues from Boston Children's Hospital summarized their experience with bivalirudin in the context of HIT [93]. The authors described their dose regimen as well as modifications required when the DTI is used. The authors suggest starting with a loading dose of 1 mg/kg followed by an infusion of 2.5 mg/kg/hour. They also recognized the need for close monitoring with repeated ACTs and dose adjustments with additional boluses of 0.5–1 mg/kg and increases in continuous infusion. That includes the following changes in CPB. The anesthesiologists must be aware that the bypass cannulas and pump suckers will be removed within a set timeframe after the discontinuation of bivalirudin. This is done to minimize the chance of blood stagnation that would lead to bivalirudin proteolysis and result in thrombosis. Because of this, blood products (cell salvage or otherwise) must be readily available for transfusion in the period immediately after separation from CPB. Modified ultrafiltration (MUF) has been safely used in several of the reported cases and should be considered when clinically appropriate; care must be taken to prevent blood stasis in the hemoconcentrator once incorporated. When used for cardiac catheterization, the authors suggest starting with a loading dose of 0.75 mg/kg

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followed by an infusion of 1.75 mg/kg/hour. It is also important to remember that although ACT is frequently used to monitor anticoagulation with DTIs, sensitivity-improving modifications are available either as point-of-care tests (e.g., Ecarin–thromboelastography) or quantitative, drug-calibrated assays (e.g., ecarin clotting time, dilute thrombin time, and chromogenic anti-IIa assays). However, these tests and assays have not been validated in the pediatric population for this application and thus should be used with caution, if at all.

In case a patient with a history of HIT requires an elective surgery, all efforts should be made to postpone the surgery until the heparin/PF4 antibody levels have become negative (±85 days). Although some experts advise not to expose those patients again to heparin, most suggest that it is safe to use heparin again due to the limited immune memory in HIT.

KEY POINTS: HEPARIN-INDUCED THROMBOCYTOPENIA

- HIT is an immune-mediated syndrome manifesting as a drop in platelet count >50% and life-threatening vascular thromboses (incidence: 30–75%)
- Clinical criteria include thrombocytopenia with a ≥50% platelet count drop or a platelet count decreases <150,000/mm^3, with or without venous or arterial thromboses.
- The treatment of clinically suspect HIT requires the interruption of any exposure to heparins, which not only includes unfractionated heparin but also LMWH and heparin-coated materials. Bivalirudin is a frequently used alternative.
- Most authors suggest that it is safe to use heparin again due to the limited immune memory in HIT.

Ultrafiltration

Ultrafiltration has been used in neonates and children undergoing cardiac surgery for many year and has been designed to minimize fluid overload, decrease the need for blood product transfusion, and reduce the plasmatic concentration of inflammatory mediators [94]. Ultrafiltration is a hemofiltration technique that passes blood through a semipermeable membrane filter and, according to a transmembrane pressure gradient, removes water, electrolytes, and other substances of small molecular size. Conventional ultrafiltration (performed during CPB) in children is associated with a statistically significant, but clinically modest, increase in the concentrations of fibrinogen and other coagulation factors [95]. MUF, which is performed after weaning from CPB, has been demonstrated to increase plasma protein concentrations and decrease postoperative bleeding and transfusion requirements [96, 97]. The efficacy of the two techniques has been discussed in a good number of articles [98–101]. In 2006, Williams and colleagues first compared clinical outcomes after heart surgery between three groups of infants with CHD that received dilutional conventional ultrafiltration, MUF, or a combination of both [102]. This study reported that the combination of MUF and dilutional conventional ultrafiltration afforded no additional benefit in terms of patient outcome relative to either dilutional conventional ultrafiltration or MUF alone. A meta-analysis of the currently available randomized controlled trials that examined the clinical benefits of MUF over conventional ultrafiltration in pediatric cardiac surgery indicated that MUF resulted in significantly higher post-CPB hematocrit levels and higher mean arterial blood pressure [103]. However, the analysis failed to show a positive impact of MUF on postoperative clinical parameters, including postoperative blood loss, ventilator time, and ICU time. These findings suggested that both MUF and conventional ultrafiltration could improve clinical conditions in the immediate post-CPB period. The benefit of MUF over continuous ultrafiltration on patient overall outcome might not be significant. In a more recent prospective randomized study, MUF was applied to all patients following the termination of CPB for either 10, 15, or 20 minutes [104]. In that study, MUF acutely improved the pulmonary compliance and gas exchange in all three groups and when lasting longer than 10 minutes acutely increased hematocrit levels and blood pressure measurements. However, there were not any additional contributions to the pulmonary, hemodynamic, and clinical measurements in the intensive care unit. Most recent guidelines recommend conventional ultrafiltration or ≥10 minutes of MUF to maximize hemoconcentration and facilitate early modification of systemic inflammatory response syndrome for neonates and infants undergoing cardiac surgery with CPB [54].

KEY POINTS: ULTRAFILTRATION

- Conventional ultrafiltration or ≥10 minutes of MUF to maximize hemoconcentration and facilitate early modification of systemic inflammatory response syndrome for neonates and infants undergoing cardiac surgery with CPB.

Management of bleeding

Cell salvage

Blood shed intraoperatively can be collected into an automated centrifuged-based blood salvage instrument that produces a heparin-free suspension of washed and concentrated RBCs. This technique can also be used to process the blood left in the CPB circuit after separation from CPB. Several meta-analyses have been published, clearly suggesting the utility of cell salvage in reducing perioperative transfusion needs in adult cardiac surgery [105, 106]. In pediatric cardiac surgery, technical limitations prevented cell salvage in smaller patients for many years. Due to the low blood volumes harvested during pediatric cardiac surgery, many commercialized cell salvage devices failed to process this low amount of blood adequately. However, recent technical advancements have made cell savers feasible for the small volume requirements of neonates and infants; therefore, cell salvage devices are now routinely used in pediatric cardiac

surgery. Two randomized clinical trials have been published and they have demonstrated the clinical utility of cell salvage in pediatric cardiac surgery through a reduction in perioperative transfusion needs [107, 108]. In addition, cell salvage has also been found to be cost-effective in pediatric cardiac surgery [109].

In clinical practice, the most common indications for the use of cell salvage are patients undergoing surgery with a high bleeding risk (e.g., re-sternotomy) and patients in which allogeneic blood transfusion is not an option (e.g., Jehovah's Witness). Some programs use cell salvage routinely and take advantage of the cell salvage technology to process CPB blood left after CPB separation. This approach is attractive as the blood at the end of CPB is usually poor-quality heparinized blood with a relatively low level of hematocrit. Processing blood with the cell salver will therefore concentrate the RBCs to higher hematocrit and eliminate heparin allowing the reinfusion of concentrated RBCs. It is however important to keep in mind that fibrinogen, platelets, and other coagulation factors will be lost in the process and will have to be replaced using the appropriate products or factor concentrates. Cell salvage can also be used to wash irradiated RBCs to reduce potassium and lactate loads and prevent hyperkalemia during CPB [110]. However, since the use of irradiated blood has been declining due to the effectiveness of leukocyte depletion, this indication has become less important during the past years.

Use of coagulation tests and transfusion algorithms

Intraoperative monitoring of hemostasis before, during, or after CPB has been studied for over 60 years. Several assays have been used either to predict bleeding or to treat coagulopathy in bleeding patients. Standard coagulation assays (e.g., activated partial thromboplastin time, aPTT; partial thromboplastin time, PTT; international normalized ratio, INR) were developed originally for the diagnosis of congenital factor deficiencies, and later the INR was formatted to guide the administration of vitamin K antagonists in both adults and children [111]. Although considered the "gold standard" of coagulation tests, these tests were not designed to monitor perioperative coagulopathy, nor to guide the administration of hemostatic agents in bleeding situations. As it usually takes 30–45 minutes to organize testing to be performed in the local hemostasis laboratory, limited information is obtained from these tests in the context of acute bleeding. In addition, standard laboratory tests are performed on platelet-poor plasma (PPP) and do not allow for a global assessment of coagulation (e.g., do not assess platelet function and fibrinolysis). Over the past decade, viscoelastic hemostatic tests have been increasingly used in different clinical conditions and are now integrated into all recent guidelines for management in adults during CPB [112–114]. Viscoelastic hemostatic assays are point-of-care tests that allow for a global assessment of coagulation at the bedside using whole blood. The technology to allow this assessment has evolved from the original thromboelastography (TEG®, Haemonetics Corp. Boston, MA) to now include thromboelastometry (ROTEM®, Instrumentation Laboratory, Bedford, MA), and, most recently, the Quantra® Hemostasis Analyzer (Hemosonics Corp., Charlottesville, VA).

In the TEG system, a cylindrical cup containing a 340 microliter whole blood sample oscillates under constant force. A pin on a torsion wire is suspended in the blood. As the viscoelastic strength of the clot increases progressively more rotation is transmitted to the torsion wire and this is detected by an electromagnetic transducer. The TEG 6s uses resonance-frequency viscoelasticity measurements and a disposable multichannel microfluidic cartridge, which decreases vulnerability to vibration and reduces user errors (Figure 16.12). In addition to the standard Global Hemostasis Cartridge, TEG 6s also includes a TEG PlateletMapping cartridge. Although the use of TEG PlateletMapping may be considered a useful supplement to the existing platelet function tests (e.g., PFA-100®, Seimens Medical Solutions, Malvern, PA; VerifyNow



Figure 16.12 TEG® 6s device and cartridge. The Global Hemostasis Cartridge includes: Kaolin TEG: intrinsic activated assay, Kaolin TEG with heparinase: intrinsic activated assay with heparinase, Rapid TEG: intrinsic and extrinsic activation, TEG Functional Fibrinogen: extrinsic pathway activated assay uses a GP IIb/IIIa platelet inhibitor to restrict platelet activity. Courtesy of Haemonetics Corp. Boston, MA.

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System™, Instrumentation Laboratory, Bedford, MA: Multiplate® Electrode Aggregometry, Roche Diagnostics, Indianapolis, IN) [115], further clinical validations will be required to define the clinical applications of TEG PlateletMapping [116].

ROTEM® uses a pin suspended on a ball bearing mechanism in which the pin oscillates through the application of a constant force. As the viscoelastic strength of the clot increases the rotation of the pin is progressively impeded and this is detected optically using a charge-coupled device (CDD) image sensor system. Different tests can be conducted simultaneously on each of the four channels of the analyzer (Table 16.4). The most recent analyzer, ROTEM® Sigma, and cartridges that contain different reagents in freeze-dried pellet form are represented in Figure 16.13.

The Quantra® QPlus System is a cartridge-based device consisting of the Quantra® Hemostasis Analyzer and single-use cartridges (QPlus Cartridge and QStat Cartridge) (Figure 16.14) [117]. The device measures shear modulus expressed in units of hectopascals (hPa) as a metric of clot viscoelastic properties during the coagulation process. This is accomplished using ultrasound generation and detection of resonance using the non-contact method of SEER (Sonic Estimation Elasticity via Resonance) Sonorheometry [118, 119]. An ultrasound pulse is sent into the blood sample causing it to resonate generating a shear wave. As the clot vibrates during resonance, returning ultrasound tracking pulses are used to measure the sample motion and create a time–displacement curve every 4 seconds. As the clot progressively stiffens the frequency of oscillations increases. The time–displacement curve at a specific point in time can be compared to theoretical models to determine the actual shear modulus.

Figure 16.15 offers a schematic representation of the TEG® and ROTEM® trace and the definition of the most important parameters are summarized in Table 16.5. Viscoelastic tests are available at the bedside and the use of TEG (TEG®, Haemonetic, Boston, MA) or ROTEM (ROTEM®, Instrumentation Laboratory, Bedford, MA) early parameters (as soon as 5 minutes after clotting time) allows for an implementation of early goal-directed hemostatic therapy in bleeding children [121]. A good correlation between viscoelastic tests and standard coagulation assays has been demonstrated in children undergoing cardiac surgery [73, 122, 123].

Diagnosis and treatment algorithms incorporating viscoelastic hemostatic tests for bleeding patients in a variety of clinical situations have now been developed. In adult cardiac surgical patients, Karkouti and colleagues conducted a pragmatic multicenter stepped-wedge cluster randomized controlled trial of a point-of-care–based transfusion algorithm in consecutive patients undergoing cardiac surgery with CPB at 12 Canadian hospitals from October 6, 2014, to May 1, 2015 [124]. In their study, the authors found that implementation of point-of-care hemostatic testing within the context of a simple, integrated transfusion algorithm across 12 hospitals reduced RBC transfusions, platelet transfusions, and major bleeding following cardiac surgery. These findings suggest that the use of point-of-care hemostatic testing improves the management of coagulopathy in cardiac surgery and support their broader adoption into clinical practice.

However, it is recognized that children, especially neonates and infants, pose different hemostatic problems on CPB when compared to adults. Of note, critical levels of hypofibrinogenemia and thrombocytopenia have been seen in infants and children, whereas this is rare in adult cardiac surgery. The efficacy of viscoelastic tests to predict bleeding in children undergoing cardiac surgery has been assessed in retrospective studies [39, 40, 125–130]. Overall, the value of intraoperative monitoring of hemostasis in predicting perioperative bleeding is weak and the vast majority of studies have failed to establish a correlation between intraoperative hemostasis parameters and the incidence of perioperative bleeding. The absence of predictive value can easily be explained by the multifactorial etiology of coagulopathy and bleeding in infants and children undergoing cardiac surgery as well the heterogeneity in terms of perioperative management, patients' co-morbidities, surgical complexity, and surgeons' individual skills and experience. The use of viscoelastic tests integrated into a well-defined algorithm to guide the use of blood products has been shown to significantly reduce blood product transfusion [131, 132]. To date, however, the efficacy of viscoelastic testing has only been studied in one prospective randomized study [133]. In this study, the

Table 16.4 ROTEM® assays and their clinical indications

Assay	Activators	Clinical indications
EXTEM	$CaCl_2$ and tissue factor	Deficiency of the factors of the extrinsic pathway.
FIBTEM	$CaCl_2$, tissue factor, and cytochalasin D	Fibrin polymerization, fibrinogen level
APTEM	$CaCl_2$, tissue factor, and aprotinin	Diagnosis of fibrinolysis when compared to EXTEM
INTEM	$CaCl_2$ and ellagic acid	Deficiency of factors of the intrinsic pathway; heparin anticoagulation
HEPTEM	$CaCl_2$, ellagic acid, and heparinase	Degree of (residual) heparinization when compared to INTEM

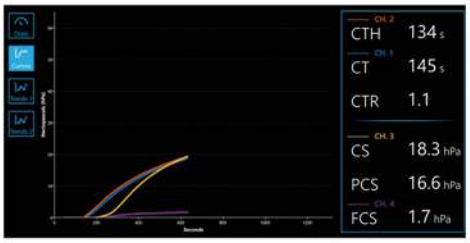


Figure 16.13 ROTEM® Sigma and cartridges. Courtesy of Instrumentation Laboratory, Bedford, MA.



Quantra® Hemostasis Analyzer





Quantra QPlus and QStat Parameters	Unit	Description	ROTEM Parameter	TEG Parameter
Clotting Time (CT) +$	Sec	Clot time measured with Kaolin activation	INTEM CT (sec)	Kaolin R (min)
Clot Time with Heparinase (CTH) +	Sec	Clot time measured with kaolin activation and with heparinase	HEPTEM CT (sec)	Heparinase Kaolin R (min)
Clot Time Ratio (CTR) +		Calculated ratio CT over CTH	Calculated ratio INTEM CT over HEPTEM CT*	Calculated ratio Kaolin R over Heparinase Kaolin R*
Clot Stiffness (CS) +$	hPA	Clot stiffness measured with thromboplastic activation and with polybrene	EXTEM MCF (mm)	TEG MA (mm)
Fibrinogen Contribution (FCS) +$	hPA	Clot stiffness measured with thromboplastic activation and with polybrene and abciximab	FIBTEM MCF (mm)	Functional fibrinogen MA (mm)
Platelet contribution (PCS) +$	hPA	Calculated from subtracting FCS from CS	Calculated from subtracting FIBTEM MCF from EXTEM MCF*	Calculated from subtracting Functional Fibrinogen MA from TEG MA*
Clot Stability Lysis $	%	Normalized difference between the CS change after maximum CS in the absence of tranexamic acid and the corresponding CS change in the presence of tranexamic acid	Ratio between lysis parameters (LY30, LY60, ML) on APTEM and EXTEM	No comparable test, but LI30 can be used on Kaolin test.

Quantra® QPlus Cartridge



Figure 16.14 Quantra® Hemostasis Analyzer, QPlus cartridge, and parameters. + QPlus cartridge provides measures of Clot Time (CT), Clot Stiffness (CS), Fibrinogen and Platelet Contributions to clot stiffness (FCS and PCS), Clot Time Ratio (CTR), and Clot Time with Heparinase (CTH). This cartridge is indicated for cardiac and major orthopedic surgery and is FDA approved in the United States. S QStat cartridge provides measures of Clot Time (CT), Clot Stiffness (CS), Fibrinogen and Platelet Contributions to clot stiffness (FCS and PCS), and Clot Stability to Lysis (CSL). The cartridge is intended for trauma and liver transplant surgery and is currently only available outside the United States. Courtesy of Hemosonics Corp., Charlottesville, VA.

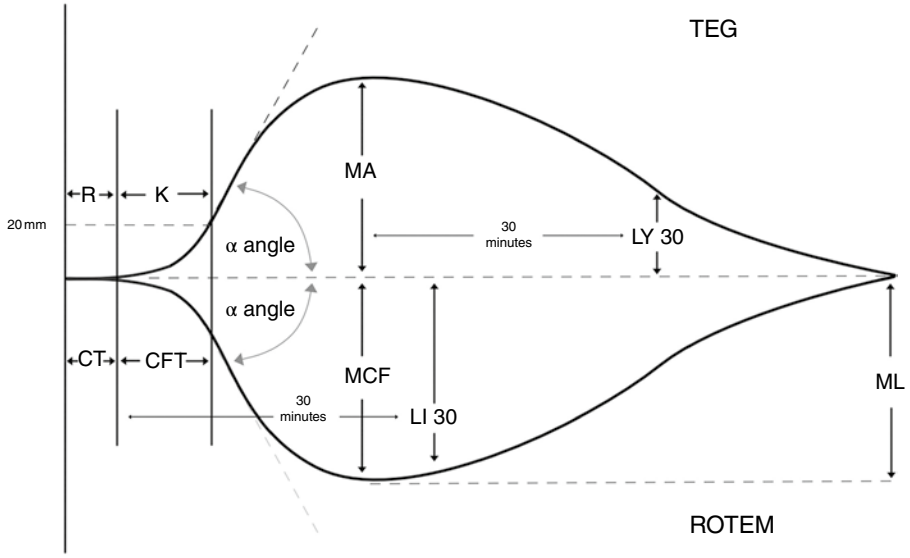


Figure 16.15 ROTEM® and TEG® trace. (Source: Haas et al. [120]. Reproduced with permission of John Wiley & Sons.)

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Table 16.5 Definition of the most important ROTEM® and TEG® parameters

	TEG®	ROTEM®	Interpretation
Clot initiation	R (Reaction time) in minutes.	CT (clotting time) in seconds.	Anticoagulation, coagulation factors deficiency
Clot kinetics	K (kinetic time) in minutes α (angle) in degrees	CFT (clot formation time) in seconds α (angle) in degrees	Anticoagulation, coagulation factors, fibrinogen, platelets deficiency
Clot strength	MA (maximum amplitude) in mm	MCF (maximum clot firmness) in mm	Platelets and fibrinogen
Clot lysis	LY30 (lysis 30 minutes after MA) in % of MA	LI30 (lysis index (residual clot firmness) 30 minutes after CT) in % of MCF ML (maximum lysis during run time) in % of MCF	Fibrinolysis

authors randomized 100 children to be managed using a conventional transfusion protocol based on routine practice ($n = 50$) or a ROTEM®-based algorithm specifically designed in that center ($n = 50$). The authors demonstrated that the application of a ROTEM®-based algorithm was associated with a significant reduction in the total amount of chest tube drainage measured at 12 hours ($p < 0.001$) and 24 hours ($p = 0.002$) after intensive care admission, and a significant reduction of the intraoperative amount of FFP and platelet concentrate administered. The authors concluded that hemostatic therapy for pediatric patients based on post-CPB thromboelastometry measurements reduced postoperative blood loss and blood product transfusion.

Only a few studies have looked at platelet function assays [9, 10, 134–137] and thrombin generation [138–140] in children undergoing cardiac surgery. None of those studies were adequately designed to assess the relationship between the intraoperative determination of platelet dysfunction or decrease in thrombin generation and transfusion or bleeding in neonates and children. Although the development of point-of-care devices to monitor platelet function (e.g., TEG® PlateletMapping cartridge) and thrombin generation could be a promising addition for intraoperative monitoring of hemostasis, further well-designed studies will be required to determine if the integration of those parameters into current transfusion algorithms could help improve perioperative management of coagulopathy and bleeding in infants and children undergoing cardiac surgery.

In the presence of ongoing bleeding, it is recommended to use intraoperative monitoring of hemostasis to guide the administration of blood products. Viscoelastic tests are better alternatives to standard coagulation assays for intraoperative bleeding management because (i) results can be obtained at the bedside within 5–10 minutes and (ii) they allow for a global assessment of clot activation, firmness, and stability [54]. Institutional algorithms should be designed based on the tests available and the availability of blood products and coagulation factor concentrates [120]. Overall, the concept of targeted therapy resides in the assessment of three components of the coagulopathy:

1. *Clot initiation* is assessed by the R time of TEG, the clotting (CT) of ROTEM®, or CT of Quantra®. Clotting times in the presence of heparinase can be used on the three devices (heparinase TEG®, HEPTEM for ROTEM®, and Clotting Time with Heparinase (CTH) of Quantra® QPlus cartridge. Those parameters can be used to estimate clotting factor deficiency and the degree of anticoagulation, including residual heparinization.
2. *Clot strength* is assessed by the clot amplitude obtained from any of those devices. The amplitude on EXTEM provides an estimate of the platelet count and fibrinogen level, the amplitude of FIBTEM provides an estimate of the fibrinogen level, and the difference between clot amplitude on EXTEM and FIBTEM provides an estimate of the platelet count. The same can be obtained from TEG® and functional fibrinogen TEG®, and the Clot Stiffness (CS) and the fibrinogen to clot stiffness (FCS) on the Quantra®.
3. *Clot lysis* can be assessed using the lysis parameters on TEG® (LY30) and ROTEM® (LI30, LI60, ML). For the Quantra®, The QStat cartridge will be needed to obtain the Clot Stability Lysis (CSL). The latter is being validated in a trauma patient [141]. It is, however, important to note that TEG® and ROTEM® are sensitive enough to detect the physiologic degree of fibrinolytic activation [142, 143], and therefore not to guide the administration of antifibrinolytic agents.

KEY POINTS: TRANSFUSION ALGORITHMS

- Although considered the "gold standard," standard coagulation tests were not designed to monitor perioperative coagulopathy, nor to guide the administration of hemostatic agents in bleeding situations.
- Viscoelastic hemostatic assays are point-of-care tests that allow for a global assessment of coagulation at the bedside using whole blood.
- Viscoelastic tests are better alternatives to standard coagulation assays for intraoperative bleeding management because (i) results can be obtained at the bedside within 5–10 minutes and (ii) they allow for a global assessment of clot activation, firmness, and stability.
- Institutional algorithms should be designed based on the tests available and the availability of blood products and coagulation factor concentrates.

Blood transfusion

The current standard of care for post-bypass bleeding includes the transfusion of adult blood products to restore hemostasis, such as packed RBCs, FFP, cryoprecipitate, and

platelets. While whole blood is available in some institutions, the transfusion of individual coagulation components is the primary treatment for post-CPB coagulopathies at most centers.

Whole blood

Historically, fresh whole blood (collected less than 24–48 hours) was used to correct the coagulopathies associated with CPB. While this practice has mostly been replaced by component therapy, there is some evidence that whole blood may be superior to component therapy in controlling bleeding after complex cardiac surgeries in children under 2 years old [35]. However, access to whole blood has been made increasingly difficult due to the techniques aimed at separating units into different components to maximize the impact of each unit. Other barriers are the logistics of timely acquiring, testing, and transporting fresh whole blood so that it is available within 48 hours of its collection.

Red blood cells

RBC transfusions are indicated for the treatment of decreased oxygen-carrying capacity causing end-organ dysfunction. This is particularly relevant for patients with congenital cardiac disease due to chronic hypoxemia (right-to-left shunting), elevated cardiac output (Qp>Qs), elevated metabolic rates, and finally the effects of surgery and CPB including hemodilution and surgical bleeding. In fact, RBC transfusions in children undergoing cardiac surgery account for more than half of all perioperative RBC transfusions.

Although RBC transfusions can be lifesaving, many studies have demonstrated an increase in morbidity and mortality associated with increasing blood transfusions. Increasing transfusions are associated with increased respiratory complications, prolonged ICU and hospital stays, decreased graft survival, increased acute kidney injury, increased thrombotic events, and immune modulation [144–148]. However, the optimal hemoglobin values for congenital cardiac surgery are not known and likely vary depending on age, degree of cyanosis, and complexity of the surgical procedure. Multiple studies have demonstrated that a restrictive transfusion practice does not increase morbidity or mortality in pediatric ICU patients, congenital cardiac patients, and preterm neonates [149–152]. However, many of the studies exclude neonates or patients with single ventricle physiology. One of the few studies examining the impact of a restrictive (hemoglobin 11.1 g/dL) vs. liberal (13.9 g/dL) RBC transfusion strategy in children with single-ventricle physiology after cavopulmonary anastomosis found no difference between the two study groups [149].

Platelet transfusion

Thrombocytopenia and platelet dysfunction are common causes of post-bypass coagulopathies and significantly increase the risk of bleeding and transfusion requirements in pediatric patients undergoing cardiac surgery. Platelet count and function in infants and children undergoing cardiac surgery are affected by CPB duration and degree of hemodilution [9, 10, 137, 153], whereas hypothermia correlates with platelet dysfunction alone [137]. A few studies suggest that the effect of CPB on platelet count and function may be age-related, with great platelet dysfunction (either activation or hypoactivity) in neonates and younger children compared with older children (Figure 16.16).

Few studies have assessed the effect of platelet transfusion on post-operative bleeding, although Romlin and colleagues completed a prospective study of 100 patients undergoing cardiac surgery comparing thromboelastography-guided transfusions versus standard management. These authors concluded that routine use of thromboelastography reduced RBC and FFP transfusions, though the rates of platelet and fibrinogen increased [131], suggesting that the primary post-CPB coagulopathies are related to platelet dysfunction. No studies to date have compared different volumes and types of platelet transfusions (e.g., concentrated or cold platelets) on post-operative bleeding. Thus, the recommendations for platelet transfusion are mainly expert consensuses, taking into account adult cardiac and pediatric transfusion guidelines [54].

Fibrinogen supplementation

A growing body of literature suggests that fibrinogen is the first coagulation factor to decrease during massive bleeding and that critically low levels are associated with post-operative blood loss and transfusion requirement in infants and children undergoing cardiac surgery [73]. During CPB, fibrinogen levels decrease up to 40% below baseline levels. However, no pediatric studies have identified the minimal plasma concentration required for adequate hemostasis. A retrospective study by Faraoni and colleagues demonstrated that plasma fibrinogen concentrations <150 mg/dL and a maximal clot firmness (MCF) on FIBTEM <3 mm predicted post-operative bleeding pediatric cardiac surgery patients [73]. Fibrinogen can be supplemented by the administration of cryoprecipitate or fibrinogen concentrate.

Although FFP can be used to replenish coagulation factors, large volumes (up to 15–30 mL/kg) are required to increase coagulation factors by as little as 20%. Such a large volume load is often not tolerated immediately after CPB in small children and may compound the coagulopathy due to further dilution of hemoglobin and platelets. As such, FFP does not contain enough fibrinogen to raise a low fibrinogen concentration to an adequate level in a child.

Cryoprecipitate is prepared by controlled thawing of FFP to precipitate and extract the coagulation factors. Cryoprecipitate contains fibrinogen (~150–700 mg/unit) as well as FVIII, FXIII, fibronectin, and vWF and has been the preferred option for fibrinogen replacement in the United States and the United Kingdom. Typically, one unit of cryoprecipitate is transfused per 5 kg of body weight and should increase the fibrinogen level by approximately 100 mg/dL [154]. In older children, 1 unit/10 kg should increase the fibrinogen concentration by approximately 50–70 mg/dL [155]. Although the risk of viral transmission is low with a single unit, the cumulative exposures needed to raise the fibrinogen level increases this risk.

An alternative to cryoprecipitate is fibrinogen concentrate (FC), a purified form of fibrinogen derived from pooled human plasma, which undergoes pasteurization to minimize

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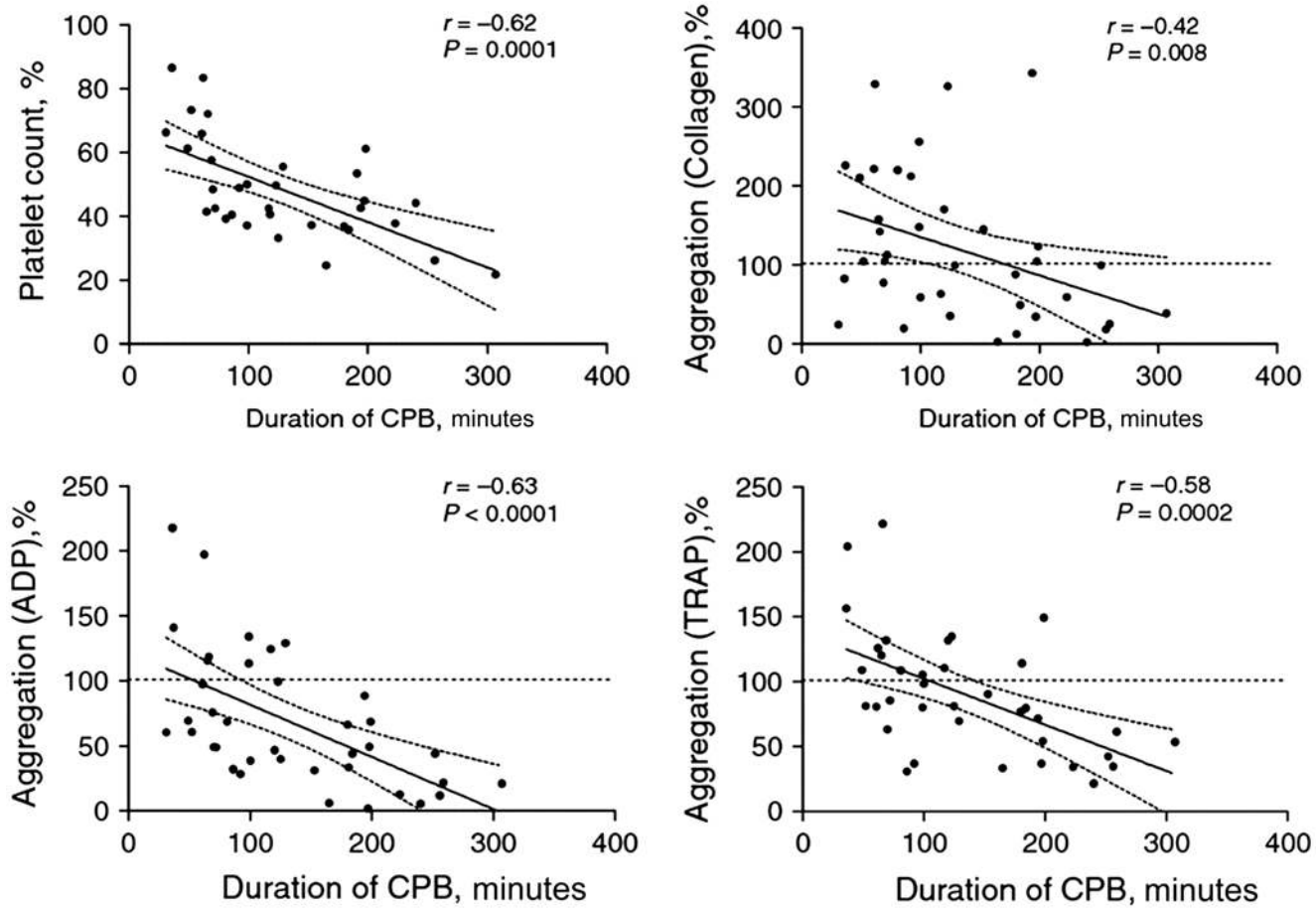


Figure 16.16 Platelet count and function decrease with increasing CPB time in pediatric patients having cardiac surgery. Platelet count and platelet aggregation after cardiopulmonary bypass. Postbypass platelet count and aggregation are plotted as a percentage of the baseline value and displayed as a function of cardiopulmonary bypass duration. a) linear regression line with 95% CI and Spearman's statistics are shown. CI: confidence interval CPB: cardiopulmonary bypass, r: rho. (Source: Andreasen [129]. Reproduced with permission of Cambridge University Press.)

the risk of immunologic and allergic reactions. In pediatric patients, FC may have several advantages over cryoprecipitate: (i) small volume, (ii) accurate dosing, (iii) immediately available, (iv) lower infectious risk, and (v) reduced allergic or immunologic reactions (Table 16.6).

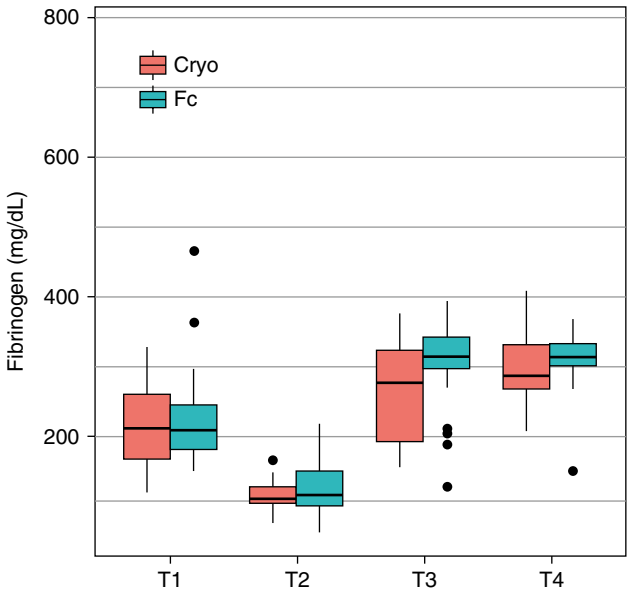
Currently, FC is being used off-label to replace low fibrinogen levels associated with bleeding in adult and pediatric surgical patients. Two small studies have investigated the efficacy and safety of FC. In a small pilot study, Galas and colleagues randomized 63 pediatric patients with a median age of 3.5 months [1–51.6 months] to receive either fibrinogen concentrate (60 mg/kg) or cryoprecipitate (10 mL/kg) after weaning from bypass if the fibrinogen levels were less than 100 mg/dL. Neither the median amount of blood loss in the first 48 hours after surgery nor the amount of allogenic blood product transfusions was significantly different between the two groups [72]. In another prospective study, Downey and colleagues randomized 60 patients <12 months undergoing cardiac surgery with CPB to receive either cryoprecipitate (2 units) or fibrinogen concentrate (target fibrinogen level ~300 mg/dL). This study demonstrated that the use of fibrinogen concentrate reduced donor exposures by 1.79 units (95% CI, 0.64–2.93) in the intent-to-treat population and 2.67 units

Table 16.6 Comparison between cryoprecipitate and fibrinogen concentrate

	Cryoprecipitate	Fibrinogen concentrate
Fibrinogen content	300–450 mg per unit	900–1100 mg/vial
Volume per unit	~300–450 mg/20 mL unit	1 g fibrinogen per 50 mL
Contents	Fibrinogen Factor VIII Factor XIII vWF	Fibrinogen
Preparation process	Stored Frozen and requires thawing ~15–17 minutes	Lyophilized powder, reconstituted with 50 mL diluent
ABO blood group Matching	Required	Not required
Viral Transmission Risks	Dependent on donor testing, no viral inactivation	Heat-treated for viral inactivation
Immune reaction risk	High – contains Immunoglobins, cytokines, cell debris	Low – Minimal immunoglobulins (low TRALI risk)

	Overall[a]	Cryo[a]	FC[a]	D
n	54	25	29	
T1				
Fibrinogen, mg/dL	210.00 [177.25, 254.75]	211.00 [166.00, 259.00]	209.00 [182.00, 245.00]	0.199
T2				
Fibrinogen, mg/dL	112.00 [100.25, 135.50]	109.00 [103.00, 128.00]	117.00 [100.00, 153.00]	0.387
T3				
Fibrinogen, mg/dL	303.00 [238.00, 337.00]	276.50 [192.25, 323.50]	314.50 [296.50, 342.50]	0.642
T4				
Fibrinogen, mg/dL	306.00 [277.00, 331.00]	286.00 [268.00, 331.00]	313.00 [299.25, 332.50]	0.011

(A)



(B)

Figure 16.17 Summary of fibrinogen levels. (A) Fibrinogen levels at different time points in each study group. (B) Box plot with distribution of fibrinogen levels in each study group at different time points. aMedian (IQR) = (25th–75th percentile). Cryo indicates cryoprecipitate arm; D, standardized difference (a measure of the difference between the distribution of the characteristic in the 2 arms expressed in units of standard deviations); FC, fibrinogen concentrate arm; IQR, interquartile range; INR, international normalized ratio; PP, per protocol. (Source: Adapted from Downey et al. [72].)

(95% CI, 1.75–3.59) in the per-protocol analysis without a significant difference in adverse events, length of stay, postoperative thrombosis, or death. The authors suggest that FC may be an adequate alternative to cryoprecipitate for pediatric patients undergoing cardiac surgery (Figure 16.17) [71]. Subsequently, the FIBRES study, involving 11 Canadian institutions, demonstrated that FC was non-inferior to cryoprecipitate in adults undergoing cardiac surgery [156].

Recommendations

- In bleeding neonates and children, guidelines recommend hypofibrinogenemia (diagnosed by either Clauss method (<150 g/dL) or viscoelastic testing) should be treated either with cryoprecipitate or FC.
- FC can be dosed in two ways:
  - 70 mg/kg or
  - Using the package insert equation to reach a target fibrinogen level:

$$\text{FC dose (mg)} = \frac{(\text{target fibrinogen} - \text{measured fibrinogen})}{1.7} \times \text{weight (kg)}$$

- Guidelines suggest that FFP should be considered for treating hypofibrinogenemia in bleeding neonates and children only when cryoprecipitate or FC is not available.

Recombinant factor VIIa

Recombinant VIIa (rFVIIa; NovoSeven® RT, Novo Nordisk, Bagsvaer, Denmark) is U.S. FDA approved for the treatment of hemophiliac patients who develop antibodies to clotting factors VII and IX. Administration of rFVIIa enhances

thrombin generation at the site of injury to facilitate the formation of a stable fibrin clot [157]. Since rFVIIa is not derived from human blood products, it has been an attractive therapeutic option for treating excessive bleeding. In fact, rFVIIa has been used "off-label" to treat excessive bleeding in a variety of clinical scenarios, including cardiac surgery.

In adults, the perioperative administration of rFVIIa after cardiac surgery has been shown to increase the risk of arterial thrombotic events [158] and in-hospital mortality [159]. In pediatric patients, rFVIIa was primarily utilized as a rescue for excessive blood loss following CPB. However, no controlled trials have been performed to assess the safety and efficacy of rFVIIa use in pediatric patients. The Congenital Cardiac Anesthesia Society organized a task force to review the literature with the intent to determine the indications for use, efficacy, safety, and appropriate dosing. Despite this large systematic review of more than 40 studies, the task force found insufficient evidence to support the use of prophylactic or routine use of rFVIIa in this patient population [160]. While rFVIIa is still used for rescue therapy at some institutions, its significant cost and lack of an established safety profile limit this appeal.

The major risk associated with rFVIIa administration is thromboembolic events. Theoretically, enhanced thrombin generation after rFVIIa is limited to the sites of vascular injury, but the thrombotic rates after "off-label" rFVIIa administration are up to 57% [160–162]. In a retrospective propensity-matched study of congenital cardiac surgery patients, those who received rFVIIa had a significantly higher thrombotic rate than those who did not (20% vs 8%) (Figure 16.18) [161]. Due to this increased risk, most guidelines recommend that the administration of rFVIIa should be restricted to rescue therapy when traditional options have been exhausted.

Recommendations

- Expert consensus recommends caution when using the administration of rFVIIa due to the thromboembolic risk.
- The recommended dosing regimen is up to two doses of 90 ug/kg administered two hours apart. Others have reported efficacy with lower doses [160, 163].

Factor concentrates

Prothrombin Complex Concentrates (PCCs) are derived from human plasma and contain coagulation factors to promote thrombin generation. They enhance coagulation by increasing the *in vivo* content of coagulation factor(s), particularly prothrombin or FII. There are approximately 15 different PCCs manufactured worldwide, but there are two main categories of PCC: 4-factor (4F) (II, VII, XI, and X) and 3-factor (3F) (II, XI, X, and very low FVII) PCC. The specific composition and amount of each clotting factor will depend on the manufacturer (Table 16.7). PCCs are approved for coagulation factor replacement therapy in patients with congenital or acquired coagulation factor deficiencies, but similar to rFVIIa, these products have been used "off-label" to manage post-CPB bleeding in pediatric cardiac patients.

In the 2005 update on oral anticoagulation guidelines, the British Committee for Standards in Hematology recommended 4F-PCC as preferential to FFP for reversing anticoagulation in patients with major bleeding [164]. In 2013, the FDA approved and recommended 4F-PCC (K-Centra, CSL Behring, King of Prussia, PA), for the reversal of vitamin K antagonists. While a few observational studies are reporting reduced bleeding and transfusion requirements after CPB in adult cardiac surgery patients, there are few studies examining this in pediatric cardiac patients. In 2020, Sisti and colleagues reported a retrospective study of 27 patients with a ventricular assist device (VAD) comparing FFP to 4F-PCC for warfarin reversal in pediatric patients undergoing orthotopic

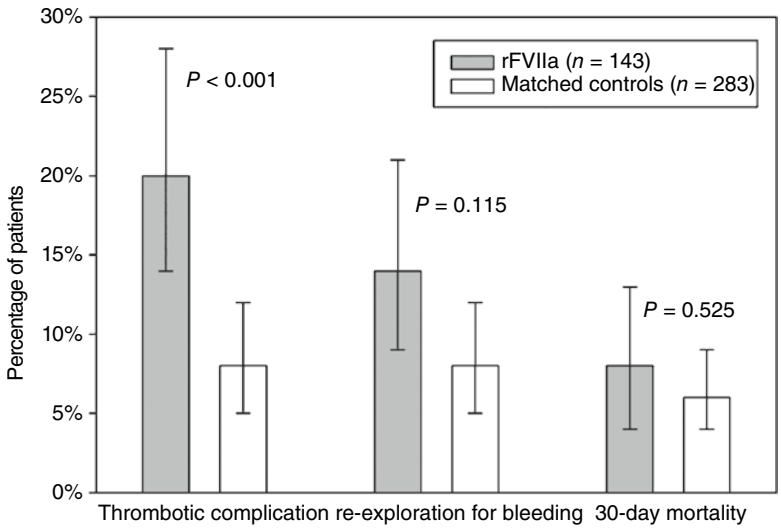


Figure 16.18 Recombinant Factors VIIa is associated with increased thrombotic complications in pediatric cardiac surgery patients. Risks of thrombotic complications, re-exploration for bleeding, and 30-day mortality. Outcome variables were compared using logistic regression analysis based on GEE to adjust for matched pairs and are reported as incidence (%) with 95% CI. $P<0.05$ was considered significant. CI = confidence interval; GEE, generalized estimating equations. (Source: Downey et al. [161]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Table 16.7 Prothrombin complex concentrates and their components available in the United States

Prothrombin Complex Concentrate	FXII	FVII	FIX	FX	Heparin	Antithrombin	Protein C	Protein S
Bebulin (Baxter International, Deerfield, IL)	+	–	+	+	+	–	–	–
FEIBA[a] (Takeda Pharmaceutical Coumpany, Lexington, MA)	+	+[a]	+	+	–	–	–	–
KCentra, Beriplex, Confidex (CSL Behring, Marburg, Germany)	+	–	+	+	+	+	+	+
Profilnine (Grifols Biologicals, Los Angeles, CA)	+	–	+	+	–	–	–	–
NovoSeven (Novo Nordisk, Plainsboro, NJ)	–	++[a]	–	–	–	–	–	–

[a] NovoSeven and FEIBA contain activated prothrombin complex concentrate available in the United States.

FII = Factor II, FVII = Factor VII, FIX = Factor IX, FX = Factor X, FEIBA = Factor Eight Inhibitor Bypassing Activity.

heart transplantation. The authors report that patients who received 4F-PCC pre-CPB received less PRBC and FFP transfusions than the control group with no difference in overall chest tube output or length of stay [165].

3F-PCC was originally approved for the repletion of factor IX in patients with hemophilia B, Factor VIII inhibitor bypassing activity (FEIBA) is a 4F-PCC with small amounts of activated FVII that was developed for hemophilia patients who developed antibodies to FVIII and FIX. Two *ex vivo* studies have looked at the effect of PCCs on optimizing thrombin generation in neonatal plasma [140, 166]. They report that 3F-PCC significantly shortened the time to initiate thrombin generation (lag time) and increased the peak amount of thrombin generated better than rFVIIa [140]. In a second study, thrombin generation in neonatal plasma was augmented by the addition of two 4F-PCC preparations (one non-activated and one activated (FEIBA)). Both PCC formulations enhanced the rate and peak amount of thrombin generation, but only activated 4F-PCC was capable of restoring lag time back to baseline values [166]. Despite these promising *ex-vivo* studies, little is known regarding the efficacy and safety of PCC use as a hemostatic agent in pediatric cardiac patients.

Although PCCs may offer several advantages, including small volumes, less immune modulation, decreased infectious risk, and improved clot formation, there are only a few published studies evaluating their clinical use in pediatric patients after CPB. In 2014, Giorni and colleagues compared the effect of PCC administered in 14 infants younger than 1 year with non-surgical post-CPB bleeding with 11 matched controls [167]. The authors showed that PCC reduced post-operative bleeding and decreased RBC transfusions without major post-operative complications. In a small case series published by Jooste et al., 3F-PCC was administered to six infants as rescue therapy for excessive post-CPB bleeding. The authors reported that PCC subjectively reduced clinically evident bleeding [168]. In 2020, Harris and colleagues published a retrospective propensity-matched study, evaluating adverse effects in patients who received 3F-PCC versus matched controls. These authors found no significant difference in the incidence of thrombosis, ECMO, or mortality. They demonstrated that platelets and cryoprecipitate administered were significantly less after the administration of 3F-PCC [169]. While all of these studies report a positive effect, questions remain regarding appropriate dosing regimens, efficacy, and safety concerns. Further clinical studies are needed before their use can be recommended in this population.

Recommendations:

- 4F-PCC should be used to reverse vitamin K antagonists in the setting of urgent or emergent surgery. Dosing regimens should follow the package insert.
- 3F- and 4F-PCC should be used for patients with congenital or acquired factor deficiencies requiring cardiac surgery with hematology consultation.
- 3F- and 4F-PCC should be used with caution in congenital cardiac surgery due to the thrombotic risk. Reported doses start at 5 mg/kg, with average doses ~10–20 mg/kg.

KEY POINTS: MANAGEMENT OF BLEEDING AFTER CPB

- Hypofibrinogenemia and platelet dysfunction are the most common causes of post-CPB bleeding.
- Treatment of post-CPB coagulopathies includes platelet transfusions and fibrinogen replacement with either cryoprecipitate or fibrinogen concentrate.
- Restrictive RBC transfusion strategies limit donor exposures and may reduce morbidity and mortality.
- rFVIIa is used off-label to enhance thrombin generation and clot formation in patients with post-CPB bleeding with anecdotal success.
- rFVIIa may be associated with an increased risk of thromboembolic events and should be used with caution.
- PCCs contain vitamin K-dependent coagulation factors in different concentrations.
- Other PCCs are being used off-label to treat excessive post-CPB bleeding, but little published data are available concerning their safety and efficacy.

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Pharmacologic therapies

Antifibrinolytics

The activation of the fibrinolytic pathway plays an important role in the coagulopathy observed during and after cardiac surgery and has prompted the prophylactic administration of antifibrinolytic agents in neonates and children undergoing cardiac surgery with CPB. During cardiac surgery, a large amount of thrombin is generated which promotes fibrinogen polymerization and thrombus formation. Thrombin also causes a conformational change such that factor XIII, α2-plasminogen inhibitor, and tissue-type plasminogen activator (t-PA) become attached to fibrin. Fibrin stimulates t-PA synthesis by endothelial cells and urokinase plasminogen activator (u-PA) synthesis by monocytes, macrophages, and fibroblasts. Both t-PA and u-PA activate plasminogen. Plasminogen can also be activated by the factor XIIa formed during the contact phase of coagulation. Plasmin is an endopeptidase that cleaves both fibrinogen and fibrin, disrupting them into fibrin degradation products (FDPs) without clotting ability. Plasmin also interacts with the inflammatory system stimulating the complement and kallikrein pathways. Fibrinolysis is inhibited by PAI 1 and PAI 2, and by thrombin binding to thrombomodulin to release and activate thrombin-activatable fibrinolysis inhibitor (Figure 16.19). Thrombin-activatable fibrinolysis inhibitor (TAFI) is the precursor of an enzyme (TAFIa) with basic carboxypeptidase activity that attenuates the lysis of fibrin clots by removal of the C-terminal lysine residues from partially degraded fibrin that mediates positive feedback in the fibrinolytic cascade [170]. Activation of fibrinolysis at CPB initiation is mainly limited to FXIIa-induced activation caused by contact of the patient's blood with the non-endothelial CPB surfaces. Fibrinolysis then becomes activated by the release of t-PA from the vascular walls. Overall, CPB results in an increase in t-PA, D-dimer, t-PA–PAI-1 complexes and a decrease in PAI-1 levels, indicating an activation of the fibrinolytic pathway and the consumption of its natural inhibitors. The degree of fibrinolytic activation is significantly correlated to the degree of thrombin generation, suggesting a strong interaction between activation of the coagulation and fibrinolytic pathways. In addition to thrombin, inflammatory markers such as cytokines and endotoxin are also able to promote the activation of plasminogen and its inhibitors. Because both plasmin and t-PA are known to interact with platelets, and vice versa, fibrinolytic activation is also associated with platelet activation [171].

Overall, fibrinolysis can be considered as a protective physiologic response that limits clot growth within a physiologic range. However, after major tissue damage and activation of CPB-induced coagulopathy, fibrinolytic activation may partially contribute to bleeding. Understanding the importance of the fibrinolytic system in CPB-induced coagulopathy and bleeding is crucial because agents capable of inhibiting fibrinolysis are available and can be administered prophylactically to avoid initiation of the fibrinolytic activation.

Antifibrinolytic agents include aprotinin and the lysine analogs (ε-aminocaproic acid [EACA] and tranexamic acid

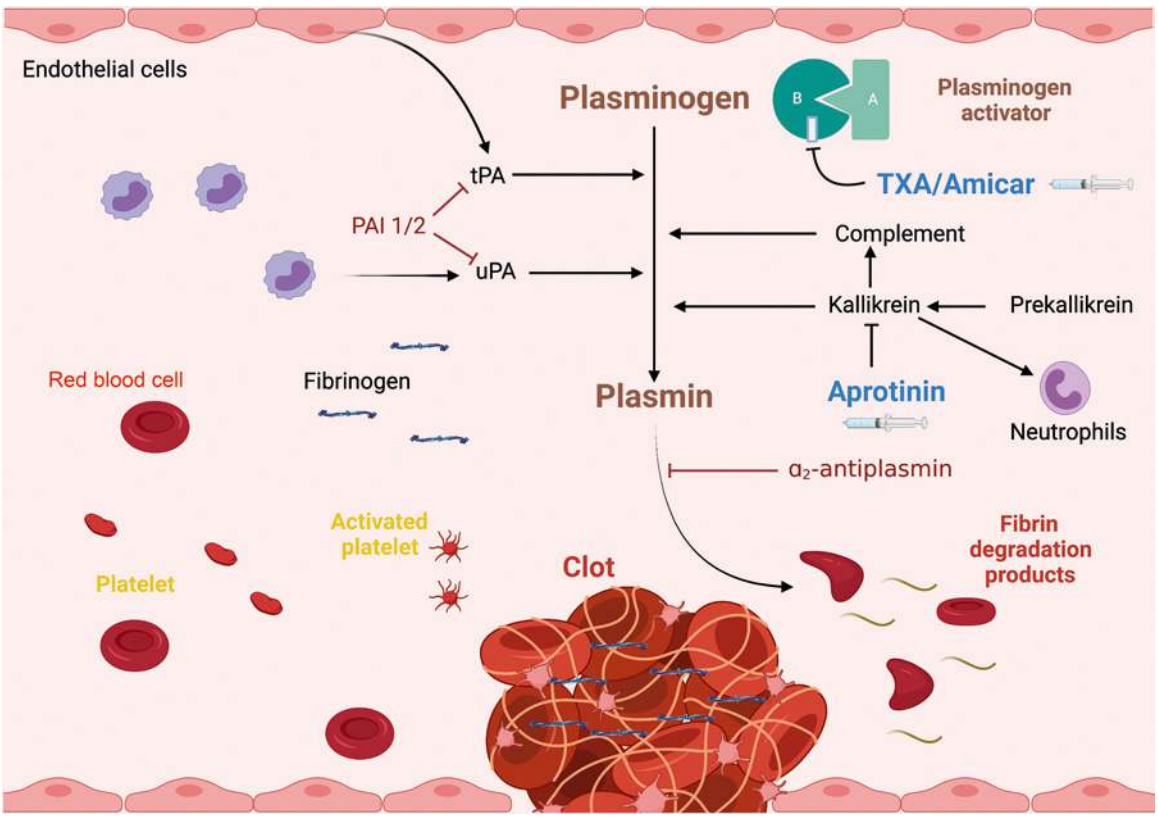


Figure 16.19 – Fibrinolysis. (Source: made in ©BioRender - biorender.com.)

[TXA]). Aprotinin is a protease inhibitor isolated from the bovine lung that is structurally similar to a tissue factor pathway inhibitor. Aprotinin is a broad-spectrum protease inhibitor that reversibly complexes with the active serine residue in various proteases in plasma (e.g., trypsin, kallikrein, plasmin, elastase). Aprotinin offers the most complete and potent fibrinolytic inhibition. Apart from these direct effects on the plasmatic coagulation system, aprotinin also inhibits the protease-activated receptor 1 thrombin receptor involved in both coagulation and inflammation. Lysine analogs, TXA and EACA, are currently the most extensively used antifibrinolytic agents. Activation of plasminogen by endogenous plasminogen activators results in plasmin, which causes degradation of fibrin. The binding of plasminogen to fibrin makes this process more efficient and occurs through lysine residues on fibrin that bind to the lysine-binding site on plasminogen. In the presence of lysine analogs, these lysine-binding sites are occupied which results in an inhibition of fibrin binding to plasminogen and endogenous fibrinolysis. Because plasmin generation after tissue injury can induce many other responses, including thrombin generation, complement activation, and activation of monocytes, neutrophils, and platelets, attenuation of these pathophysiologic responses with lysine analogs might provide additional benefits in restoring hemostatic balance, plasmin generation, and fibrinolysis.

Until 2007, aprotinin was the most frequently used antifibrinolytic agent. In 2007, the efficacy of aprotinin and other lysine analogs was summarized in a Cochrane systematic review and meta-analysis [172]. When compared to placebo, both aprotinin (77 studies), TXA (29 studies), and EACA (10 studies) significantly reduced the exposure to allogeneic blood products in adults undergoing cardiac surgery. Even though a trend in favor of aprotinin was observed, no statistical difference was reported when aprotinin was compared to TXA. No difference in terms of adverse events was reported when antifibrinolytic agents were compared to placebo or to each other, but none of the studies were actually designed to assess the safety of the drugs. Prospective studies that assessed the efficacy and safety of aprotinin in neonates and children undergoing cardiac surgery are rare. In a meta-analysis published by Schouten and colleagues in 2009, 18 studies were identified but only one study compared the efficacy of aprotinin and EACA [173]. Other authors have compared TXA and aprotinin in children but failed to demonstrate the superiority of one drug among the other.

In 2007, the results of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study, a prospective study performed in high-risk patients undergoing cardiac surgery, were published [174]. This study reported an increased incidence of mortality associated with aprotinin (6% 30-day mortality for aprotinin) when compared to lysine analogs (3.9% for TXA and 4% for EACA). The publication of the study was followed by an FDA warning and in November 2007, Bayer Health- care (Leverkusen, Germany) announced the withdrawal of aprotinin from the market.

Several respective studies looked at the effect of aprotinin on the incidence of postoperative renal dysfunction or mortality in neonates and children. Among all those studies, two large retrospective analyses failed to demonstrate any evidence of increased mortality or renal failure in children undergoing cardiac surgery. While aprotinin appeared to be non-superior to EACA, TXA was shown to be superior to aprotinin in terms of transfusion with less morbidity. The safety of aprotinin was re-evaluated in several retrospective studies in adult cardiac surgery with conflicting results, but the overall impression is that the risk of adverse events is essentially observed when aprotinin was administered in a subset of the cardiac population and that the drug remains beneficial when used in patients undergoing procedures with high bleeding risk. In September 2011, Health Canada and in February 2012, the European Medicines Agency (EMA) lifted the suspension of aprotinin from the market. Aprotinin should only be given during primary coronary artery bypass grafting surgery and should be avoided in patients with preoperative renal dysfunction due to increased risks of postoperative renal failure and the requirement for renal replacement therapy. To date, no decision has been taken regarding the use of aprotinin in neonates and children undergoing complex cardiac surgery. However, in the absence of evidence regarding the safety of the drug in the pediatric cardiac population, lysine analogs should be preferred.

The efficacy of prophylactic administration of the lysine analogs in neonates and children undergoing cardiac surgery with CPB has been studied in several small prospective studies. In a systematic review and meta-analysis that compared TXA to placebo, prophylactic administration of TXA reduced the need for blood product transfusion [175]. All the prospective studies published to date have included a relatively small number of patients presenting with heterogeneous congenital heart diseases and undergoing procedures of variable complexities. Significant variability in dosages has been reported, with some centers using three boluses of 10 to 100 mg/kg, while others used a 10 to 100 mg/kg loading dose followed by a continuous infusion. Another important limitation of the current literature is the absence of safety assessment when sometimes large doses of antifibrinolytics are administered. To date, adverse reactions have only been reported in small retrospective studies while none of the prospective studies were designed or powered to look at the incidence of side effects. If no risk of thrombotic complication has been reported in the adult or pediatric literature, an increased risk of clinical seizures has been described following the administration of high-dose TXA. Lecker and colleagues showed that TXA inhibits neural glycine receptors, whereas inhibition of the inhibiting neurotransmitter glycine is an established cause of seizures [176]. Viewing the similarities in the chemical structures of TXA, gamma-aminobutyric acid (GABA), and glycine, it is conceivable that the interaction of TXA with both GABA and glycine receptors contributes to the increase in clinical seizures observed when TXA is given. Interestingly, the TXA peak concentration observed in the cerebral spinal fluid was reached approximately 5 hours after the plasma peak concentration (Figure 16.20), which might explain the delay reported between TXA administration and the development of clinical seizures after cardiac surgery. Similar concerns have also been described with equipotent concentrations of EACA, which might be explained by the fact that EACA is a competitive agonist of glycine receptors. Understanding pharmacology is crucial, and the use of a pharmacokinetic/pharmacodynamic-based dose regimen should be promoted.

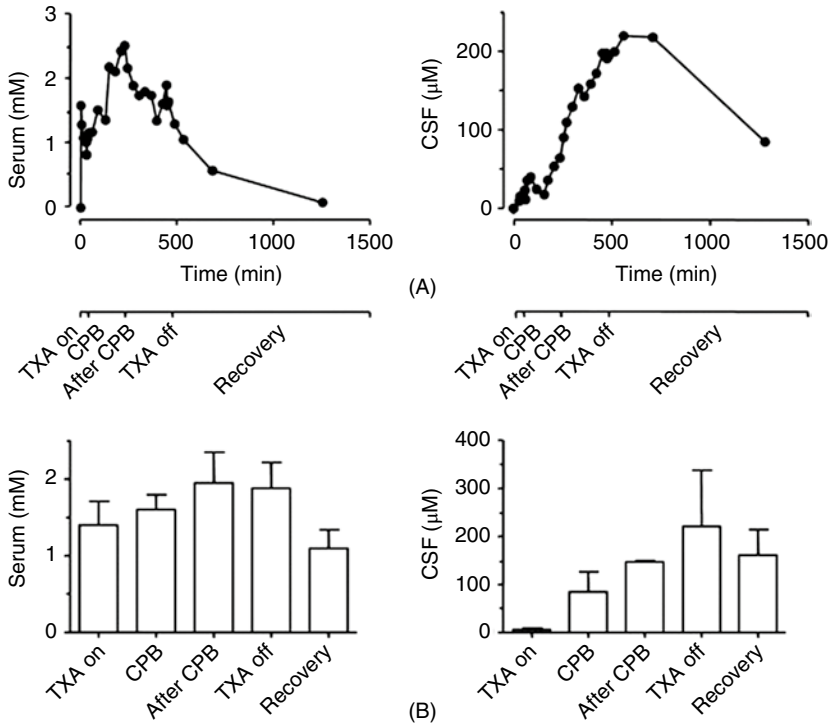


Figure 16.20 TXA concentrations measured in the serum and CSF of patients who underwent cardiopulmonary bypass and major vascular surgery. (A) Time-dependent plot of TXA concentration in the serum and CSF of one patient. The timeline at the bottom of the figure represents key surgical events. (B) Average TXA concentration in the serum and CSF during key surgical events (n = 4). Data are mean ± SEM. (Source: Lecker et al. [176]. Reproduced with permission.)

The gap in our understanding of the pharmacokinetics of lysine analogs in neonates and children has been partially filled by the publication of a few pharmacokinetic studies [177]. In 2002, Ririe and colleagues studied the pharmacokinetics of EACA in 8 patients aged between 9 months and 4 years [178]. As a result, the authors suggested a dosing regimen of 75 mg/kg over 10 minutes, 75 mg/kg on CPB, and 75 mg/kg/hour infusion started at the end of the initial bolus. This regimen was derived and simulated to maintain serum concentration at two times the serum levels to produce 95% efficacy (260 μg/mL). In 2015, Eaton and collaborators studied the PK of EACA in 10 neonates undergoing cardiac surgery with CPB [179]. Simulations were performed to maintain plasmatic concentrations of 50 μg/mL, leading to the recommendation of a 40 mg/kg loading dose followed by a 30 mg/kg/hour infusion. The authors suggested the administration of 10 mg of EACA per liter of CPB prime. Those two dosing regimens demonstrated the large variability in targeted plasma concentrations (50 μg/mL vs. 260 μg/mL) and the need for further studies to determine the optimal plasma concentration to be targeted to safely inhibit fibrinolytic inhibition using EACA in neonates and children. One of the first pediatric cardiac TXA PK studies was published by Grassin-Delyle and colleagues in 2013 [180]. In their study, the authors randomized 21 patients to receive either a continuous infusion (10 mg/kg followed by a 1 mg/kg/hour with 10 mg/kg at CPB initiation) or discontinuous infusion (10 mg/kg, then 10 mg/kg into the CPB and 10 mg/kg/hour initiated at the end of CPB). From their pharmacokinetic modeling, the authors determined the most appropriate dosing scheme to obtain a given target concentration of 20 μg/mL in children weighing 5 to 40 kg. The recommended 6.4 mg/kg loading dose is identical for all children, whereas the infusion rate decreases with weight from 3.1 mg/hour/kg to 2.0 mg/hour/kg for children between 5 and 40 kg, respectively. In 2015, the second pharmacokinetics (PK) study was published by Wesley and colleagues [181]. In their study, the authors included 55 patients ranging from 2 days to 4 years old and categorized them into three groups: children less than 2 months old, infants 2 months to 1 year old, and children greater than 1-year-old and weighing up to 20 kg. The authors described three different dose regimens based on targeted plasmatic concentrations (e.g., 20, 60, or 150 μg/mL). In order to maintain a plasmatic concentration of 60 μg/mL, a loading dose of 50 mg/kg followed by a continuous infusion of 7 mg/kg/hour was suggested in neonates and infants <2 months of age, a loading dose of 26 mg/kg followed by a continuous infusion of 6 mg/kg/hour was suggested in infants aged from 2 to 12 months, and a loading dose of 13 mg/kg followed by a continuous infusion of 5.5 mg/kg/hour was suggested in children >12 months and ≤20 kg. An additional bolus of 60 mg/mL of prime volume was also suggested (Table 16.8).

Despite the major advances made in the understanding of lysine analogs PK in neonates and children undergoing cardiac surgery, the readers will appreciate the persisting variability among the different PK-based dose regimens. This variability is mainly explained by the lack of knowledge regarding the minimal concentration required to inhibit

Table 16.8 Summary of the dose regimens suggested in pharmacokinetics studies

Study	Population	Targeted concentration	Loading dose	Infusion	CPB
1. ε-aminocaproic acid					
Eaton [179]	2.7–3.7 kg	50 μg/mL	40 mg/kg	30 mg/kg/hour	10 mg/L
Ririe [178]	9 months–4 years	260 μg/mL	75 mg/kg	75 mg/kg/hour	75 mg/kg
2. Tranexamic acid					
Grassin-Delyle [180]	5–40 kg	20 μg/mL	6.4 mg/kg	2.0 to 3.1 mg/kg/hour	NA
Wesley [181]	0–2 months	20 μg/mL	15 mg/kg	2.5 mg/kg/hour	20 mg/L
	2–12 months	20 μg/mL	9 mg/kg	2 mg/kg/hour	20 mg/L
	>12 months (Max 20 kg)	20 μg/mL	4 mg/kg	2 mg/kg/hour	20 mg/L
	0–2 months	60 μg/mL	50 mg/kg	7 mg/kg/hour	60 mg/L
	2–12 months	60 μg/mL	26 mg/kg	6 mg/kg/hour	60 mg/L
	>12 months (Max 20 kg)	60 μg/mL	13 mg/kg	5.5 mg/kg/hour	60 mg/L

fibrinolytic activation in children undergoing cardiac surgery with CPB. On the basis of the initial investigations published in the 1970s, two basic target concentrations have been identified. A lower concentration of approximately 10–20 μg/mL, which is thought to inhibit approximately 80% of fibrinolysis, and a high concentration of approximately 100 μg/mL, which should completely inhibit fibrinolysis. For several reasons, and in particular the difficulty of accurately measuring fibrinolytic activation in-vivo, those plasmatic concentrations have never been clinically validated. To date, only *ex-vivo* t-PA-activated models of hyperfibrinolysis have been used to estimate the plasmatic concentration required to completely inhibit fibrinolytic activation in neonates and children [182, 183]. If the plasmatic concentrations obtained from those *ex-vivo* models appeared to be significantly lower than the one described in the 1970s (<20 μg/mL), further studies are needed to further validate the findings in neonates and children undergoing cardiac surgery.

Based on the existing literature, a TXA loading dose of 30 mg/kg followed by a continuous infusion of 10 mg/kg/hour can be used in children <1 year of age, while loading dose of 10 mg/kg followed by a continuous infusion of 10 mg/kg/hour can be used afterward. For EACA, a loading dose of 40 mg/kg followed by a 30 mg/kg/hour infusion is recommended [54].

Desmopressin

Desmopressin (DDAVP) is a vasopressin analog that increases circulating levels of coagulation factor VIII and von Willebrand factor (vWF) by stimulating the release of stored vWF from the Weibel Palade bodies in the endothelium. It has been hypothesized that DDAVP favors the hemostatic process not only by inducing the release of vWF from endothelial cells but also by enhancing the procoagulant activity of platelets [184]. When platelets encounter a damaged vessel wall, they immediately recognize and adhere to exposed collagen and other subendothelium proteins. The adherent platelets become activated and recruit other platelets to the site of vascular injury. Meanwhile, the initiation of the coagulation cascade generates thrombin, which further activates platelets. By the combined action of thrombin and collagen, platelets express on their surface a number of specific molecules that promote both thrombin formation and cell-cell interactions (COAT platelets). It has been suggested that desmopressin infusion enhances the formation of COAT platelets and thus improves the hemostatic activity of platelets [185].

Desmopressin is used mainly to improve hemostasis in patients with von Willebrand disease, hemophilia A and certain inherited disorders of platelet function. In a recent Cochrane review, 39 studies were identified in the adult cardiac population where DDAVP was administered after cardiopulmonary bypass. In adults undergoing cardiac surgery, the reduction in the volume of RBCs transfused and total blood loss was small and was unlikely to be clinically important [186]. The efficacy of desmopressin in reducing bleeding and transfusion in children undergoing cardiac surgery has only been assessed in 3 studies [187–189]. The administration of DDVAP was not associated with a significant reduction in blood loss or blood product transfusion. However, the studies published to date preferred a prophylactic administration of DDAVP without estimation of the bleeding risk, the platelet count, vWF levels, and platelet function. Further studies are needed to study the effect of DDAVP administration post-CPB in children with normal platelet count ($\geq 150 \times 10^9$/L) but with decreased platelet function and/or in patients with acquired vWF deficiency.

KEY POINTS: PHARMACOLOGIC THERAPIES

- Prophylactic administration of antifibrinolytic drugs helps decrease bleeding and transfusion in pediatric cardiac surgery.
- High doses should be avoided to decrease the risk of side effects, especially clinical seizures with TXA.
- Further studies are needed to study the effect of DDAVP administration post-CPB in children with normal platelet count ($\geq 150 \times 10^9$/L) but with decreased platelet function and/or in patients with acquired vWF deficiency.

Sickle cell disease

Sickle cell disease (SCD) is a genetic disorder of hemoglobin and is characterized by hemolysis and recurrent vaso-occlusive episodes that cause severe pain "crises" and lead to progressive

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organ dysfunction. Patients with SCD only produce Hemoglobin S (HbS), which contains abnormal beta chains. Unlike normal adult Hemoglobin A (HbA), HbS is unstable in hypoxic conditions and polymerizes into the long helical strands that give affected RBCs the "sickled" appearance. These sickled RBCs have a shorter life span (10–12 days) than normal RBCs (120 days), which leads to chronic hemolytic anemia. During periods of dehydration, physical exertion, infection, or the stress of surgery can precipitate a sickle cell crisis. These "sickled" RBCs occlude blood flow to organs and lead to vaso-occlusive events (pain crises) and end-organ damage. Long-term complications from SCD include chronic anemia, pulmonary hypertension, or ischemic strokes.

Cardiac surgery presents numerous challenges that require special consideration for SCD patients due to hypothermia, CPB circuit primes, and prolonged NPO times. However, cardiac surgery with CPB has been undertaken successfully in SCD patients. Patients scheduled for cardiac surgery should have an outpatient visit with a hematologist 2–4 weeks prior to the procedure for evaluation and transfusion planning.

Preoperative laboratory studies should include at least a CBC and type and screen. In addition to a type and screen, consider obtaining an RBC genotype testing for extended antigen matching, as it can be challenging to find appropriate blood products for patients receiving chronic transfusions. Prior to surgery, it is important to communicate to ensure that appropriate blood is available for the procedure. Some institutions will send hemoglobin electrophoresis and reticulocyte count. Patients with an HbS ≥30% or a total hemoglobin <10 g/dL, these patients may require preoperative admission for hydration and an exchange transfusion.

The goal of intraoperative management is to avoid conditions that would result in sickling of the RBCs, such as hypoxia, hypothermia, or emotional stress. The goal is to minimize the percentage of HbS to ≤30% to reduce the risk of sickling. Therefore, patients with elevated HbS may require an exchange transfusion at the initiation with cardiopulmonary bypass. Prior to the exchange transfusions, it is important to maintain adequate oxygenation and maintain normothermia. Other considerations to minimize RBC trauma include maintaining bypass flow, minimizing pump sucker trauma, and vasodilating the patients with isoflurane or phentolamine as tolerated. Although systemic hypothermia and cold cardioplegia have been used, normothermia is preferred when possible. Finally, adequate post-operative pain management is critical but can be challenging in SCD patients. A multi-modal approach that includes opioids, acetaminophen, and Non-steroidal anti-inflammatory drugs (NSAIDs) should be employed. Consider regional anesthesia if possible.

KEY POINTS: SICKLE CELL PATIENTS FOR CARDIAC SURGERY

- SCD is a genetic disorder of hemoglobin (homozygous HbS) that is characterized by vaso-occlusive episodes that result in pain crises and end-organ damage.
- Dehydration, hypoxia, infection, physical exertion, hypothermia, or the stress of surgery can all precipitate a sickle cell crisis.
- For patients coming for cardiac surgery, the goal of management is to avoid or minimize factors that may precipitate a sickle cell crisis. Patients may require an exchange transfusion to decrease the percentage of HbS ≤30%.
- These patients often present with preoperative anemia; it may be difficult to find cross-matched blood due to chronic transfusions and alloimmunization.

Summary

Perioperative management of coagulopathy and hemostasis in neonates and children undergoing cardiac surgery is complex. Preoperative optimization of RBC mass should be promoted, as well as the implementation of blood conservation techniques. Maintenance of adequate anticoagulation during CPB, rapid assessment of coagulopathy, and the implementation of transfusion institutional algorithms based on monitoring of coagulopathy and the use of targeted therapy are keys. Despite the progress made in the last decades, further clinical studies are urgently needed to assess the safety and efficacy of the most recent diagnostic and therapeutic options.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

18 Brown AC, Hannan RT, Timmins LH, et al. Fibrin network changes in neonates after cardiopulmonary bypass. Anesthesiology 2016;124(5):1021–31. The authors examine the sequential changes in clotting components and resultant clot structure in a small sample of neonates undergoing cardiac surgery and cardiopulmonary bypass.

29 Odegard KC, Zurakowski D, DiNardo JA, et al. Prospective longitudinal study of coagulation profiles in children with hypoplastic left heart syndrome from stage I through Fontan completion. J Thorac Cardiovasc Surg 2009;137(4):934–41. The authors describe changes in coagulation factors over time in children with hypoplastic left heart syndrome.

41 Zabala LM, Guzzetta NA. Cyanotic congenital heart disease (CCHD): focus on hypoxemia, secondary erythrocytosis, and coagulation alterations. Paediatr Anaesth 2015;25(10):981–9. This review summarizes the coagulopathy of cyanotic congenital heart disease with a specific focus on hypoxemia and secondary erythrocytosis.

42 Jones SE, Jooste EH, Gottlieb EA, et al. Preoperative laboratory studies for pediatric cardiac surgery patients: a multi-institutional perspective. Anesth Analg 2019;128(5):1051–4. This statement published by the members of the hemostasis interest group (HIG) of the congenital cardiac anesthesia society (CCAS) discuss variability in prative when it comes to preoperative laboratory testing.

54 Faraoni D, Meier J, New HV, et al. Patient blood management for neonates and children undergoing cardiac surgery: 2019 NATA guidelines. J Cardiothorac Vasc Anesth 2019;33(12):3249–63. Guidelines published for blood management and blood conservation in neonates and children undergoing cardiac surgery.

71 Downey LA, Andrews J, Hedlin H, et al. Fibrinogen concentrate as an alternative to cryoprecipitate in a postcardiopulmonary transfusion algorithm in infants undergoing cardiac surgery: a prospective

randomized controlled trial. Anesth Analg 2020;130(3):740–51. Prospective randomized study assessing the efficacy of fibrinogen concentrate versus cryoprecipiate for fibrinogen supplementation in children undergoing cardiac surgery.

78 Dieu A, Rosal Martins M, Eeckhoudt S, et al. Fresh frozen plasma versus crystalloid priming of cardiopulmonary bypass circuit in pediatric surgery: a randomized clinical trial. Anesthesiology 2020;132(1):95–106. In this prospective randomized study, the authors demonstrated that the use of fresh frozen plasma in the cardiopulmonary bypass prime did not reduce bleeding and transfusion when compared to crystalloids in children weighting 7–15 kg.

134 Nakayama Y, Nakajima Y, Tanaka KA, et al. Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. Br J Anaesth 2015;114(1):91–102. Prospective randomized study of the effect of the implementation of a ROTEM-based transfusion algorithm in children undergoing cardiac surgery.

167 Downey L, Brown ML, Faraoni D, et al. Recombinant factor VIIa is associated with increased thrombotic complications in pediatric cardiac surgery patients. Anesth Analg 2017;124(5):1431–6. Propensity matched analysis highlighting the increased risk of thrombotic complications assiciated with the use of rFVIIa.

188 Wesley MC, Pereira LM, Scharp LA, et al. Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2015;122(4):746–58. Pharmacokinetic study of tranexamic acid in neonates and infants undergoing cardiac surgery with suggestions for dose regimen based on three targeted plasma concentrations.

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CHAPTER 17

Point-of-Care Ultrasound for Congenital Heart Disease Patients

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Introduction

Use of point-of-care ultrasound (POCUS) in acute care practice has expanded to include a variety of applications from ultrasound-assisted physical examination to assessment of hemodynamic states as well as guidance for procedures. Within anesthesia practice, POCUS may be used to guide management at all stages of perioperative care [1]. While the list of applications for POCUS within anesthesia practice is growing, this chapter focuses on the cardiac and lung POCUS with an emphasis on patients with congenital heart disease (CHD). See Chapter 13 for a discussion of ultrasound-guided vascular access and Chapter 24 for a presentation of ultrasound-guided regional anesthesia.

What is POCUS?

POCUS is the systematic application of ultrasound performed at the bedside to evaluate specific structures, generally using a limited number of ultrasound views [2]. Clarity of language is paramount when describing the various ultrasound modalities examining the heart. Ultrasound evaluation of the heart has become a continuum of imaging devices and strategies ranging from limited evaluations with miniaturized handheld devices to comprehensive imaging of the heart with large cart-sized devices on wheels with the highest resolution medical ultrasound technologies [3]. Some consider the very limited evaluations of the ultrasound of the heart to be more like an extension of the physical examination rather than a stand-alone imaging test [4]. In many ways, these distinctions are still being created in modern cardiac imaging, but standard echocardiography remains the most comprehensive ultrasound-based evaluation of cardiac anatomy and function [5]. Cardiac POCUS and focused cardiac ultrasound seem to be the best terms, which are currently being used interchangeably to describe more targeted cardiac ultrasound evaluations. For consistency, the authors are using the term cardiac POCUS.

During this imaging strategy, a bedside clinician (most often a noncardiologist) uses ultrasound to examine the heart in a limited fashion with a goal to identify a limited number of specific ultrasonographic signs that are which could be associated with the clinical situation of interest or a specific pathology [6]. While cardiac POCUS is almost always performed with a smaller, more portable ultrasound machine

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with limited functionality, it should be defined by the imaging technique rather than the machine used [7, 8]. Since cardiac POCUS has narrowed diagnostic targets with focused questions, it is important to clearly distinguish it from comprehensive standard echocardiography during medical documentation or communication between providers. Confusion can be created if ambiguous terms, such as "bedside echo or limited echo," are used to describe clinician-performed cardiac POCUS. The term echocardiography (or similar forms) should be reserved for more comprehensive evaluations, usually performed by a cardiac sonographer and often include quantitative measurements. Whereas cardiac POCUS should be limited to a few predefined views where the clinician can make qualitative assessments. With non-precise language, the assumptions of broader diagnostic targets or evaluations can occur creating misunderstanding or false reassurances. See Chapters 15 and 18 for further discussion of comprehensive echocardiography.

Pediatric cardiac POCUS

The evidence supporting the accuracy of cardiac POCUS by noncardiologists in pediatrics comes predominantly from small single center studies with mostly structurally normal hearts [9–13]. The identification of severely depressed systolic function and larger effusions are the most reliable findings [14]. Given how cardiomyopathy and severely depressed ventricular systolic function can present in pediatrics with insidious onset and/or with misleading chief complaints, cardiac POCUS seems to have a valuable role to play in the early identification of severely depressed left ventricular systolic function [15]. However, borderline systolic dysfunction is the area of significant weakness [9, 16]. Some argue that borderline systolic dysfunction may be out of the scope of pediatric cardiac POCUS [13]. Users of pediatric cardiac POCUS should be keenly aware of this weakness of the modality. This is particularly important in pediatrics since borderline depressed function in a previously healthy child is often a harbinger of rapidly progressive cardiogenic shock, especially in infectious myocarditis or inflammatory disorders [17, 18]. There is scant evidence supporting cardiac POCUS in more complex CHD, and its use in this population should be limited to those with extensive training and experience in CHD training and/or pediatric echocardiography. Additionally, the use of cardiac POCUS as *a screening tool* for CHD is likely counterproductive and it is likely contraindicated for this purpose [14].

The diagnostic targets for pediatric cardiac POCUS are typically limited to the assessments of ventricular size, qualitative ventricular systolic function, right ventricular systolic pressure, and the pericardial space [14]. Evaluation of diagnostic targets is performed in a qualitative or semiquantitative manner, typically using an "eyeball" method [2, 8, 14]. These assessments are usually binary, i.e., is there pathology present or is there not? Declaration of uncertainty is often the correct approach in POCUS if the diagnostic targets are not well visualized, particularly given the inherent nature of POCUS. Cardiac POCUS image acquisition and interpretation are performed rapidly (less than 5 minutes) and usually in suboptimal imaging conditions. Quality improvement work in pediatric transthoracic echocardiography has shown that the conditions in which POCUS is performed – incomplete examinations outside the echocardiography laboratory, in poor ambient light conditions via lower end machines with increased acoustic artifacts – are the exact setup for diagnostic errors [19]. Therefore, a low threshold for referral for standard echocardiography seems reasonable when using cardiac POCUS to clarify equivocal imaging or to evaluate persistent symptoms after an unrevealing cardiac POCUS. Inability to diagnose disease using substandard imaging equipment in suboptimal imaging conditions does not prove the absence of disease.

Basic physics of POCUS

The ultrasound technology for POCUS is based on the same principles of physics as routine ultrasonography. The top of the ultrasound probe contains crystals (piezoelectric crystals) in various configurations based on the type of probe and its intended clinical use. The ultrasound machine transmits an electrical impulse, which results in vibration of these crystals. It is this vibration that emits a sound wave that travels into the adjacent tissue. Sound is absorbed, scattered, and reflected by the tissues. Sound reflected by the tissues returns to the probe where it results in vibration of the crystals. This mechanical vibratory energy is converted to electrical energy, which is processed to create an image.

Ultrasonic waves are refracted and reflected differently by tissues based on their various densities. The speed at which these sound waves are traveling when returning to the probe is converted to an image that is color coded in grayscale. The depth of the structure is determined by the time it takes from the wave transmission until the reflected sound wave returns. Image color may be darkened or lightened using the gain function of the machine. In contrast, air does not conduct sound waves (including ultrasonic waves) well. This limits the abilities of cardiac POCUS during situations involving pneumomediastinum or pneumothorax. Additionally, lung ultrasound relies more on observing artifacts and scatter from lung structures that generate certain ultrasonographic signs indicative of normal and pathologic conditions.

Most modern machines are equipped with complex software that is designed to reduce artifacts which is of benefit when scanning solid structures (e.g., the heart and liver). However, when scanning lung tissue, this feature should be turned off as artifact is vital to image interpretation. Many machines have pre-settings in which image quality is optimized for the structure of interest.

Ultrasound machines have probes of different configurations, sizes, and with a wide range of frequencies. The frequency of the ultrasonic wave emitted is inversely proportional to the amplitude of the wave and hence the resolution. Therefore, a higher frequency probe, with a lower amplitude, is able to delineate structures more finely. On the other hand, waves with higher amplitude attenuate more slowly as they travel through tissue. Therefore, a higher frequency, lower amplitude probe is able to penetrate to a lower depth in the body, while a lower frequency probe is able to penetrate to a greater depth, e.g., in obese habitus or deeper

structures. Depending on the brand of ultrasound equipment, a range of frequencies may be available with capabilities between 3 and 8 Hz. Cardiac POCUS is typically performed using a phased array probe while lung POCUS relies on a linear array probe (Figures 17.1 and 17.2). Providers should consider the size (space between ribs) of the patients and object of interest (e.g., lung or heart) when selecting a probe.

Performing cardiac POCUS

Basic cardiac POCUS relies on four main views. These are generally performed while the patient is supine with the exception of the apical four-chamber view that benefits from left lateral decubitus positioning. Each ultrasound machine has a specific method for indicating the probe side also known as the orientation marker, which is located on the side of the probe.

Parasternal long-axis view

The parasternal long-axis (PLAX) view is obtained with the probe in the second left intercostal space with the orientation marker facing toward the patient's right shoulder (10 o'clock position). The top of the screen depicts the anterior aspect, and the right and left of the screen are directed toward the feet and head of the patient, respectively. Visualized in this view are left atrium, left and right ventricles, aortic and mitral valves, and left ventricular and a portion of the right ventricular outflow tracts (Figure 17.3).



Figure 17.1 Varying sizes of phased-array probes for use in cardiac point-of-care ultrasound. Arrows indicating the orientation marker.

Parasternal short-axis view

The parasternal short-axis (PSAX) view is obtained by rotating the probe 90° clockwise from the PLAX view, so the orientation marker points toward the patient's left shoulder (2 o'clock). This view may be optimized by moving the probe up or down one rib space. Visualized in this view are the right and left ventricles, the cardiac apex, and the mitral valve (Figure 17.4).

Apical four-chamber view

The apical four-chamber view is obtained by placing the probe in the fourth or fifth intercostal space along the anterior axillary line with the orientation marker facing toward the left (3 o'clock position). Visualized in this view are the right and left atria and ventricles and the atrioventricular valves (Figure 17.5).

Subcostal four-chamber and inferior vena cava views

The subcostal four-chamber view is obtained with the probe in the subxiphoid space, with the probe facing the patient's left axilla and orientation marker on the oriented at 2–3 o'clock position (Figure 17.6). To obtain the inferior vena cava (IVC) view, the probe is rotated counterclockwise, so that it is vertical with the orientation marker facing straight up. Visualized in the subcostal four-chamber view are the right and left atria and ventricles and the atrioventricular valves. Visualized on the IVC view is the liver, intrahepatic IVC with entrance into the right atrium as well as the hepatic veins (Figure 17.7).

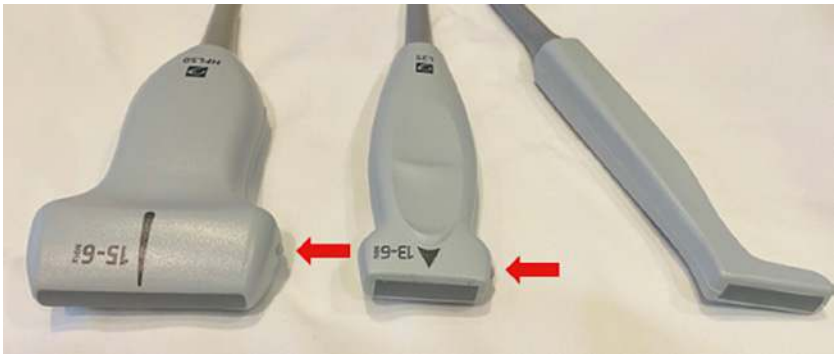


Figure 17.2 Linear-array probes for use in lung point-of-care ultrasound. Arrows indicating the orientation marker.

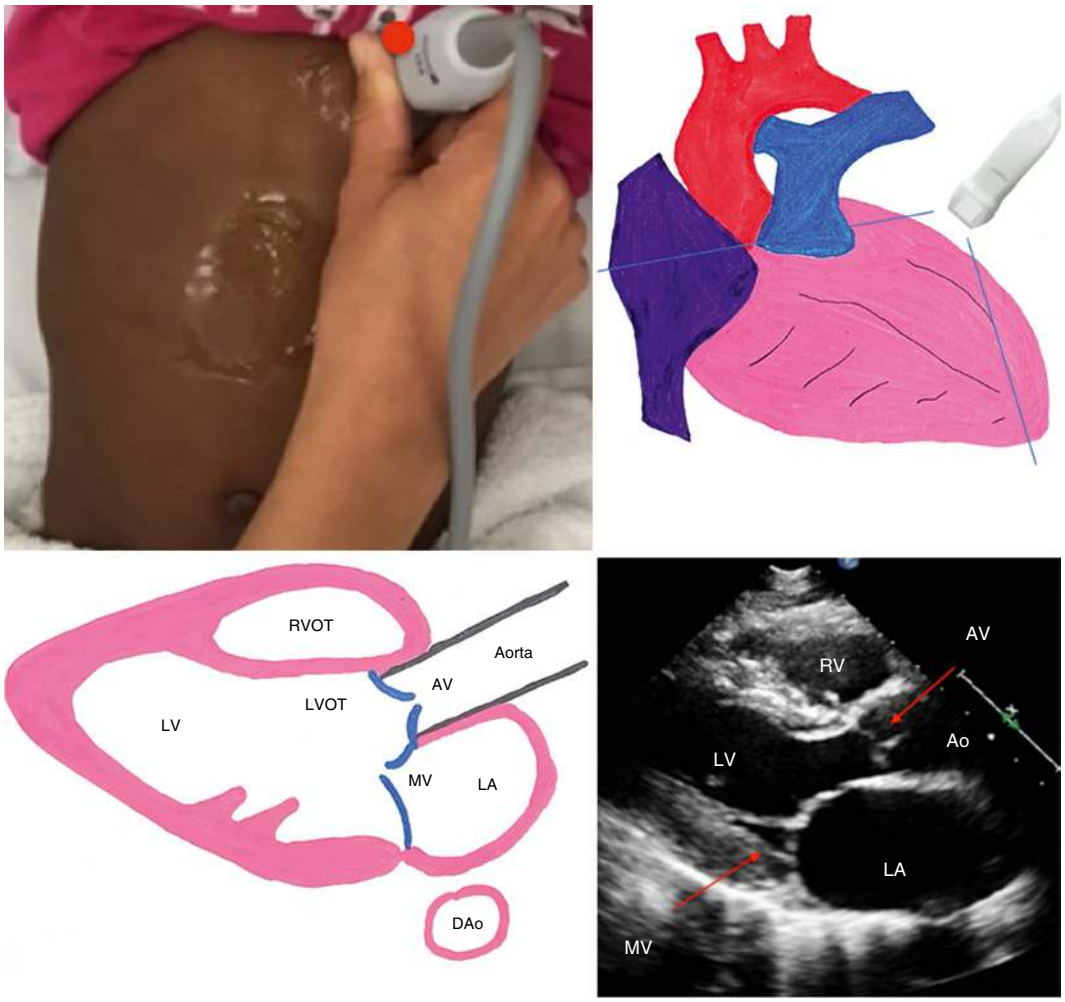


Figure 17.3 Demonstration of the parasternal long-axis view including probe placement (upper left) with red dot denoting orientation marker, scanning plane (upper right) and accompanying diagram (bottom left) and ultrasonographic appearance (bottom right). RV = right ventricle, LA = left atrium, LV = left ventricle, MV = mitral valve, TV = tricuspid valve, AV = aortic valve, Ao = aorta, LVOT = left ventricular outflow tract, RVOT = right ventricular outflow tract. Dao = descending aorta. Illustration by A. Adler, MD.

Individual structure assessment using cardiac POCUS

In the following section, the common structures evaluated during cardiac POCUS are discussed. A key requirement of POCUS, and specifically cardiac and lung assessments, is for the provider to recognize normal from abnormal. This requires deliberate training and review of images, so that the sonographer is able to distinguish and identify ultrasonographic signs of pathology from normal sonoanatomy.

Assessment of the left ventricle

Systolic dysfunction—Perhaps, the most common use of POCUS in children, including those with CHD, involves the assessment of systolic function. This may be prompted by new onset hypotension in the perioperative period, presentation in shock and concern for cardiogenic etiology, or new onset ventricular arrhythmias. This assessment permits further clinical decision-making including choice of vasoactive agent, next steps of resuscitation, possible need for activation of mechanical support team, or need for further advanced investigations. All typical cardiac POCUS views can be employed to assess left ventricular systolic function, but PSAX and PLAX views are more commonly employed views to utilize eyeball or quantitative methods. It is important to note that children who have undergone ventricular septal defect repair with patch will have dyskinesis of the part of the interventricular septum that is composed of patch material. The nuances of this cannot be worked out on cardiac POCUS and would need a formal echocardiogram. Also, operators must recognize that cardiac POCUS will give information only about systolic dysfunction and is not intended for diastolic dysfunction.

Qualitative or eyeball method assessment via ultrasound is best supported for the evaluation of left ventricular size and systolic function. While the method is inherently subjective, it compares quite well with more objective parametric measures of left ventricular systolic function when employed

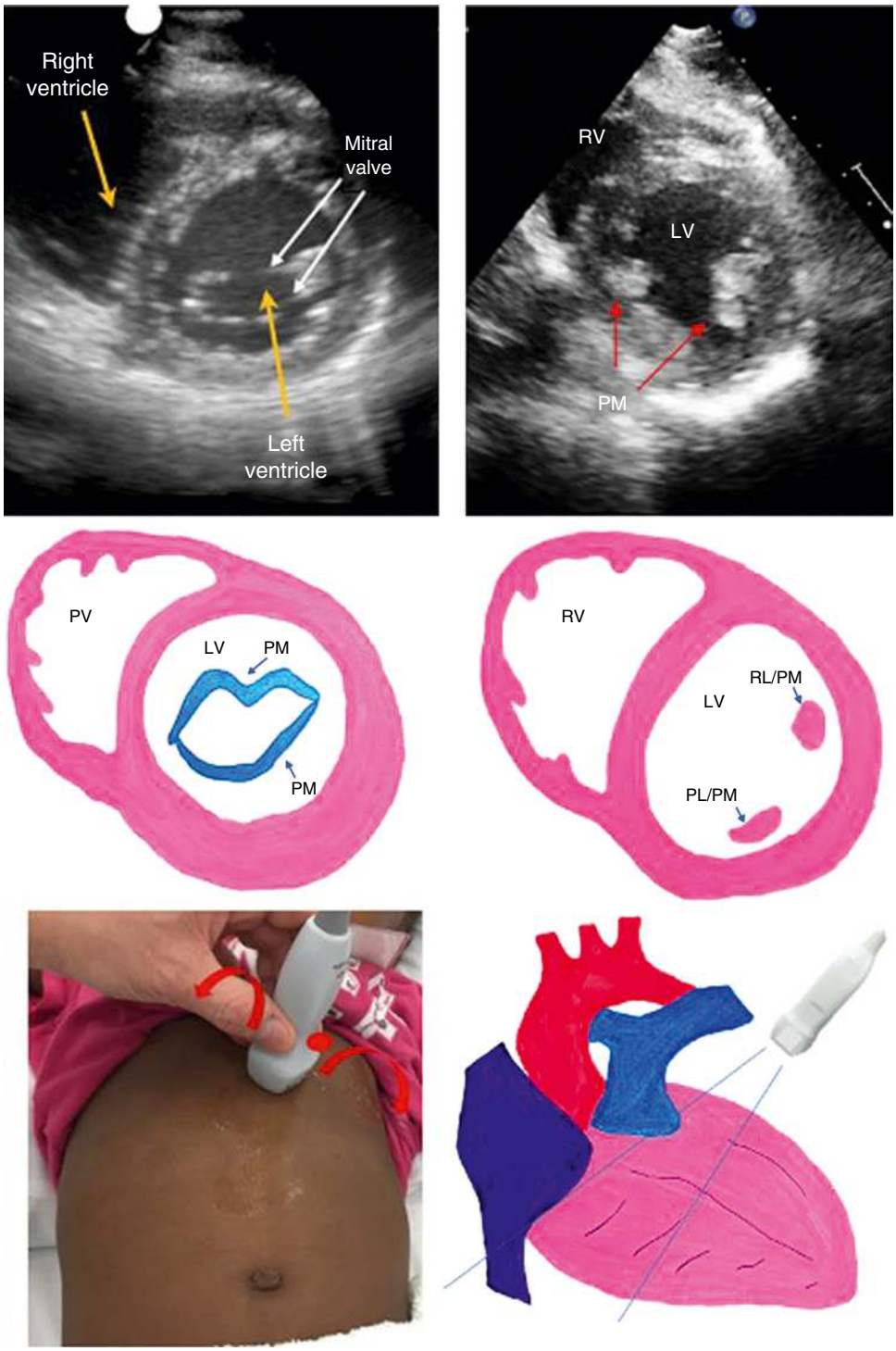


Figure 17.4 Demonstration of the parasternal short-axis view including ultrasonographic appearance at the level of the mitral valve (upper left) with accompanying diagram (middle left) and at the level of the papillary muscles (upper right) with accompanying diagram (middle right) as well as probe placement (bottom left) with orientation marker (red dot) and suggested fanning planes (red arrows) and corresponding scanning lines (bottom right). RV = right ventricle, LV = left ventricle, PM = papillary muscle, ALPM and PMPM = anterolateral and posterior medial papillary muscles respectively. Illustration by A. Adler, MD.

by experienced users [20]. For the novice user, the qualitative assessment of ventricular systolic function can be broken down into the evaluation of how well the ventricular walls are thickening and how well the ventricular walls are symmetrically moving towards the center of the cavity [21]. Precise estimation or quantification of ventricular ejection fraction is out of scope for cardiac POCUS, but novel users should know when evaluating the ventricular wall "squeeze" toward the center that the left ventricle normally ejects about 55–70% of its contents with each contraction. The decrease in

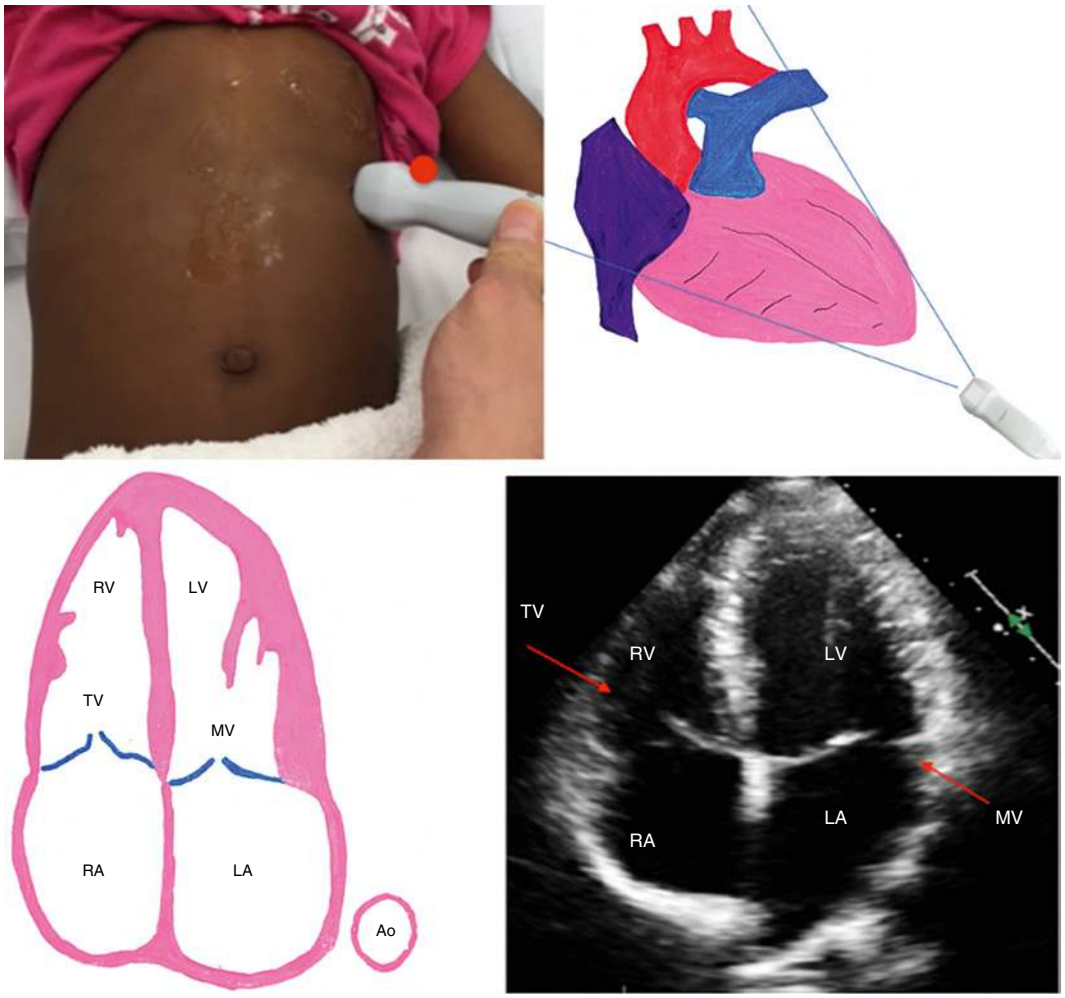


Figure 17.5 Demonstration of the apical four-chamber view including probe placement (upper left) with red dot denoting orientation marker, scanning plane (upper right) and accompanying diagram (bottom left), and ultrasonographic appearance (bottom right). RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, MV = mitral valve, TV = tricuspid valve, Ao = aorta. Illustration by A. Adler, MD.

chamber size is largely created by the thickening of ventricular walls during contraction. Making sure that the ventricular walls are actually contracting is important, because there can be misleading scenarios with poor imaging windows where the heart is moving or "rocking" on the screen, but there is ineffectual ventricular wall contraction and the chamber size decrease is difficult to evaluate.

While tracking the ventricular wall motion, it can be helpful to note that the left ventricle normally employs a relatively even combination of longitudinal, circumferential, and radial wall motions, resulting in a fundamental twisting and untwisting type of ventricular wall movements [22]. Accurate tracking of the types of wall motion is out of the scope of cardiac POCUS and is used in higher order echocardiography image packages, namely, speckle tracking or strain imaging. However, the user should be generally aware of the how left ventricular walls move in this coordinated fashion during normal contractions.

POCUS assessments of left ventricular systolic function should be limited to whether systolic function is normal, abnormal, or unclear. There may be value in identifying somewhat depressed left ventricular systolic function in pediatrics, but it is not clear at this point if this is a reliable POCUS practice. Repeated exposure to variable degrees of left ventricular systolic function via image libraries can help novice users improve their proficiency diagnosing ventricular dysfunction [22]. Quantification (e.g., shortening fraction, ejection fraction, E-point separation) during POCUS is generally avoided since incorrect measurements are common in rapid image acquisition and can potentially solidify false impressions of cardiac size or performance [8].

Assessment of the right ventricle

The right ventricle's anterior position below the chest wall and its complex geometric shape with thin walls are the main challenges to interrogate it via transthoracic ultrasound [22]. Therefore, the assessment of the right ventricle in cardiac POCUS is typically more limited than other structures and, at times, is not possible.

Right ventricular enlargement often accompanies right ventricular strain or pressure or volume loading, therefore can be helpful if present to identify right heart pathology [22]. But, the absence of right ventricular dilation by cardiac

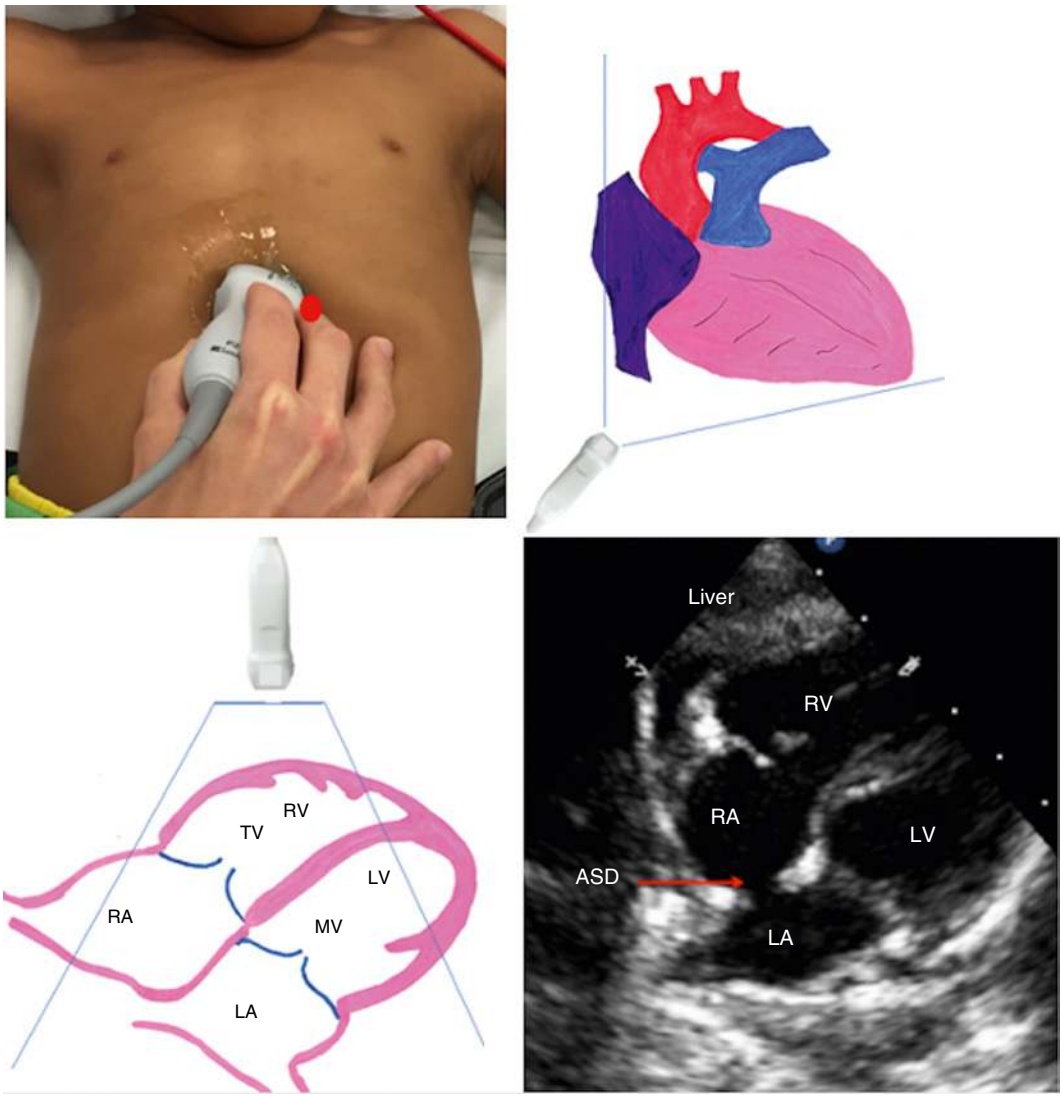


Figure 17.6 Demonstration of the subcostal four-chamber view including probe placement (upper left) with red dot denoting orientation marker, scanning plane (upper right) and accompanying diagram (bottom left), and ultrasonographic appearance (bottom right). RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, MV = mitral valve, TV = tricuspid valve. Illustration by A. Adler, MD.

POCUS does not suggest the absence of right heart pathology, likely since large portions of the right ventricle may not be adequately visualized and pathologic dilation can be missed [23]. Qualitative assessment of right ventricular size is based mostly on the comparison of size to adjacent structures (assuming the absence of pathology of the adjacent structures, such as left ventricular dilation). In the PLAX views, a portion of the right ventricle body can be seen just below the transducer. As a general rule of thumb, the diameters of the right ventricular body, aortic root, and left atrium in the PLAX view should roughly be the same. In PSAX and apical four chamber views, the right ventricle should appear about ⅓ to ½ the size of the left ventricle [23].

Even with experienced echocardiographers, eyeball assessment of right ventricular systolic function by ultrasound has been shown to be less reliable as compared to the left ventricular systolic function evaluation [23]. Some limited evaluations of the right ventricular systolic function are possible employing a similar approach to evaluating the left ventricle, again, based on how well the ventricular walls are thickening and how the ventricular walls are moving toward the center of the cavity. When evaluating ventricular wall motion, it is important to note that the right ventricle systolic contractions have more longitudinal wall motion (annulus to apex) than the left ventricle [23]. This longitudinal wall motion of right ventricular contraction is typically best seen from apical four-chamber views when the tricuspid valve moves toward the apex and transducer. Additionally, parasternal and subcostal views offer limited assessment of right ventricular wall contractions. Subcostal views of the right ventricle can be valuable, if available, in critically ill patients who do not have adequate apical or parasternal views because they cannot be repositioned on their side.

Interventricular septal configuration can be evaluated by POCUS and used as a correlate of right ventricular health and pressures [14]. Interventricular septal configuration reflects the relative pressure between the two ventricles throughout

the cardiac cycle and thus provides qualitative insight to right ventricular pressure estimates. In general, when the right ventricle pressures are less than ½ of the left ventricular pressure, the interventricular septal configuration should have a rounded appearance with the convex aspect directed into the lower pressure right ventricle [23]. Flattening of the interventricular septal configuration is suggestive that the right ventricular pressures are greater than ½ of the left ventricular pressures at that moment of the cardiac cycle. Diastolic flattening of the interventricular septal configuration typically represents a right ventricular volume load or an elevated right ventricular end-diastolic pressure [23]. Systolic flattening of the interventricular septal configuration represents a right ventricular pressure load or an elevated right ventricular systolic pressure. The differential diagnoses for flattening of the interventricular septal configuration can be narrowed by timing of flattening, but it remains broad, e.g., pulmonary hypertension, CHD, and pulmonary embolism. Most POCUS exams will not utilize simultaneous ECG readings; therefore, pinpointing the timing of the septal flattening within the cardiac cycle can be difficult, particularly during live scanning in critical scenarios. Additionally, false appearance of interventricular septal flattening can be easily created during off-angle PSAX views. For these reasons, we recommend that any flattening of the interventricular septal configuration should therefore prompt referral for standard echocardiography and more in-depth cardiac evaluation.

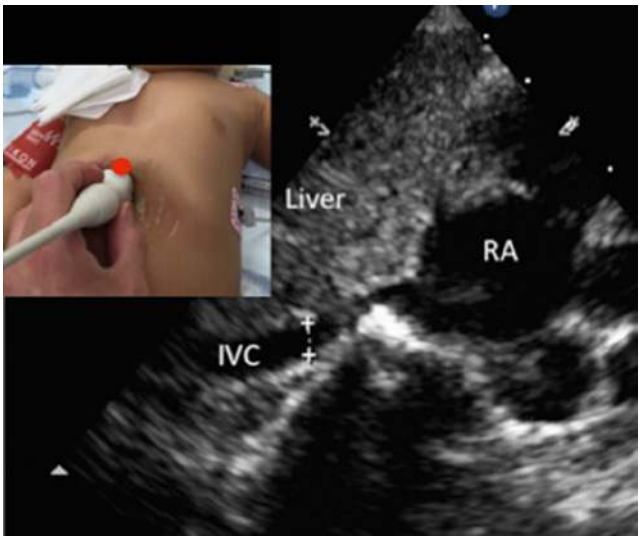


Figure 17.7 Demonstration of the inferior vena cava (IVC) view including ultrasonographic appearance and probe placement (insert) in which the IVC can be visualized entering the right atrium (RA).

Assessment of pericardial space and early tamponade physiology

The early diagnosis of pericardial effusions in children is a valuable aspect of pediatric cardiac POCUS [14]. Physical examination is insensitive to the condition and chest radiograph is unable to make the final diagnosis. A pericardial effusion resulting in tamponade physiology impervious to medical therapy should prompt referral to a skilled interventionalist [23].

The pericardium is typically visible in ultrasound evaluations of the heart, recognizable by the bright echogenic line surrounding and closely abutting the myocardium in physiologic conditions. With buildup of excessive pericardial fluid, an echo-lucent or black area can be seen via ultrasound beginning to build between the myocardium and pericardium. It is important to evaluate whether that the effusion is within the pericardial space since adjacent pleural effusions can be present or coexist (Figure 17.8). Subcostal views can help differentiate these potential spaces and identify concomitant issues such as other effusions (Figures 17.8 and 17.9). On PLAX views, evaluating the relationship of the echo-lucent fluid collection between the pericardium and the

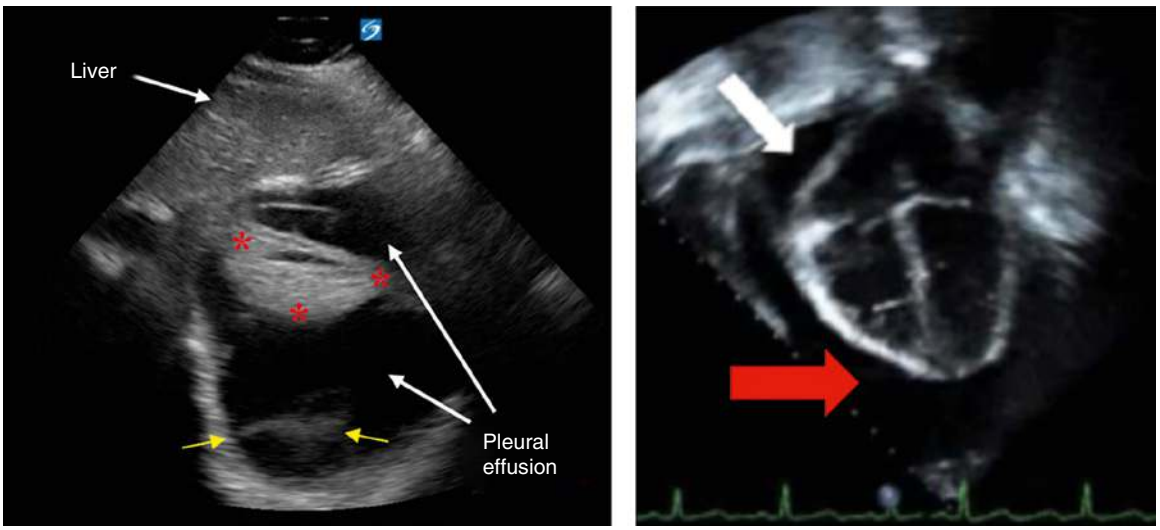


Figure 17.8 POCUS imaging demonstrating (A) large pleural effusion with lung consolidation (red stars) and fibrinous exudate (yellow arrows) and (B) apical four-chamber view with large circumferential pericardial effusion (red arrow) and right atrial collapse (white arrow). (Source: Adler et al. [32]. Reproduced with permission from Springer Nature.)

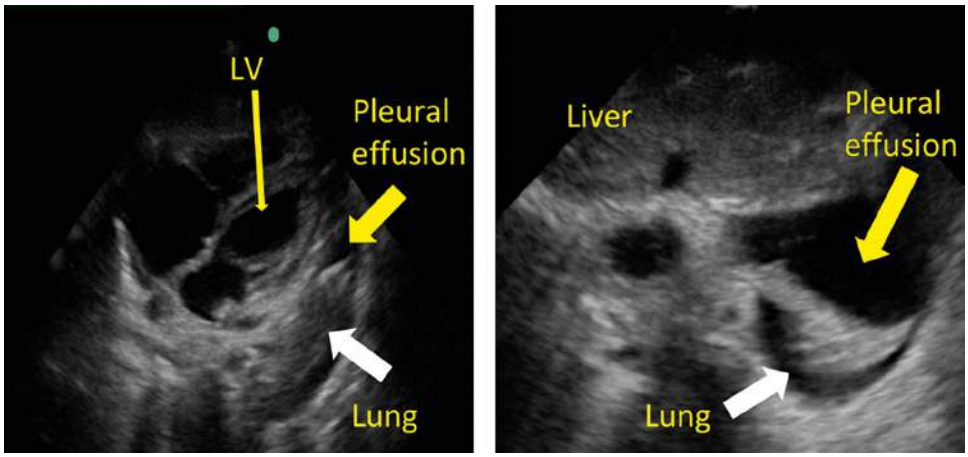


Figure 17.9 (A & B): Subcostal four-chamber view with large pleural effusion and lung consolidation, LV = left ventricle. (Source: Adler et al. [40]. Reproduced with permission from John Wiley & Sons.)

descending aorta can provide good information of the location. The descending thoracic aorta is a structure outside the pericardium; therefore, some pleural effusions can be in continuity with the descending aorta seen in its short axis behind the cardiac mass. On the other hand, no pericardial effusions will be in continuity with descending aorta [23].

The pericardium is composed of elastic fibers and collagen into visceral and parietal layers. The pericardial sac is able to slowly expand with chronic effusions, but it is inextensible beat-to-beat and during rapid accumulation of pericardial fluid. Therefore, a rapid accumulating, even relatively small, pericardial effusion is more likely to result in an inward force and eventual tamponade physiology as compared to a slowly evolving pericardial effusion seen in some medical diseases [23]. Pericardial pressure is negligible in physiologic conditions. But, as a pericardial effusion enlarges, pericardial pressure will eventually begin to elevate. As pericardial pressure rises, it can begin to overcome intracardiac pressures during certain nadirs in the chambers' cardiac cycles, resulting in partial collapse or indentation, which can be seen via cardiac POCUS. The right heart chambers that tend to have lower pressure in general, therefore, are the first chamber to demonstrate collapse with worsening pericardial effusion. The right atrium will most likely start to show collapse during ventricular systole, as this is the typical nadir of the right atrial pressure during the cardiac cycle. The right ventricle will most likely start to show collapse during ventricular diastole, as this is its nadir [23]. These early phases imply impaired cardiac filling and onset of tamponade physiology. Therefore, one of the earliest physiologic responses to a significant pericardial effusion is tachycardia due to the inadequate preload. There is the caveat of coexisting pathologic arrhythmias, such as sinus node dysfunction. True tamponade is when the pericardial pressures overcome all cardiac pressures and blood is unable to circulate through the cardiopulmonary system despite normal ventricular systolic and diastolic function. Medical therapies and chest compressions are essentially useless in this scenario, with needle compression being the definitive therapy [23]. Therefore, again, timely diagnosis prior to frank tamponade is of paramount importance and concerns for large or hemodynamically significant effusions diagnosed by cardiac POCUS should prompt urgent formal echocardiographic and/or interventionalist evaluation.

It is important to remember that not all pericardial effusions are circumferential. They can be loculated or localized in certain areas of the pericardial space, potentially impacting adjacent heart chambers. Localized, particularly rapidly accumulating pericardial effusions can be just as hemodynamically active as a larger circumferential effusion. This is can be seen in postoperative or postprocedural situations or if there are adhesions within the pericardial space. Careful assessment of the whole pericardial space via long sweeps of the heart is important in cardiac POCUS, particularly if there is clinical concern for hemodynamically significant pericardial effusion. The best long sweeps to assess for effusions in cardiac POCUS are usually obtained in subcostal views, sweeping either posterior to anterior (coronal views) or left to right (short axis).

Assessment of the atria and valves

A qualitative view of the atria should be appreciated when performing cardiac POCUS. Most notably, providers should observe that the atria do not appear large or compressed. Similar to ventricular assessment, the provider should attempt to distinguish atria as normal or abnormal. Additionally, the presence of a large thrombus can be identifiable, even to the novice sonographer. However, small thrombi that may be clinically significant can be missed.

With regard to valvular assessment, the atrioventricular and semilunar valves may be observed for obvious structural deformity, stenosis, or regurgitation. While not typically part of basic cardiac POCUS, limited assessment using color Doppler can aid an overall assessment of stenosis or regurgitation. Assessments should be limited, qualitative in nature, and should attempt to discern if a clinically significant pathology is present. Ruling out pathologic atrioventricular valve dysfunction is likely out of the scope of POCUS.

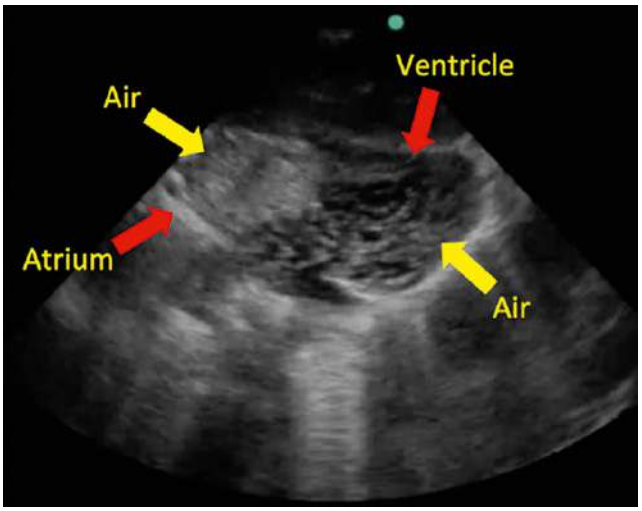


Figure 17.10 Subcostal four-chamber view showing a large volume of air microemboli after inadvertent injection of air during cardiac catheterization in a 4-month-old with hypoplastic left heart syndrome, resulting in arterial desaturation, hypotension, bradycardia, and ST-segment elevation. The patient recovered after 2 boluses of epinephrine of 1 mcg/kg and fluid bolus of 20 mL/kg. (Source: Adler [34]. Reproduced with permission from Elsevier.)

Assistance during cardiac arrest

POCUS is valuable during cardiac arrest in identifying reversible causes of cardiopulmonary collapse as well as assessing the likelihood for achieving return of spontaneous circulation (absence of intrinsic cardiac function). The subcostal four-chamber view can be performed during cardiopulmonary resuscitation at times where chest compressions are paused for pulse checks. In this view, the provider can identify intrinsic cardiac function and presence of large pericardial effusions. The chest may also be scanned to evaluate for pneumothoraces which may be under tension and the case of the cardiopulmonary arrest. In addition, intracardiac air can be easily visualized as a cause of hemodynamic instability or cardiac arrest (Figure 17.10) [24].

Assistance during central line placement

The use of modified cardiac POCUS has been described for assistance with central line placement and positioning in children. Park YH et al. described the use of POCUS to guide central line depth in infants undergoing congenital heart surgery [25]. Specifically, they describe the use of longitudinal images of the right atrium and superior vena cava in addition to obtain a pulmonary bifurcation view allowing for imaging of the right atrium [25]. Alternatively, the right ventricular inflow view can also serve to aid in the visualization of proper central line positioning. While these views do not fall within basic POCUS, this highlights the ability for deliberate expansion of this modality to aid in the care of patients.

Specific clinical situations and corresponding limitations

As described above, cardiac POCUS can yield key information in several clinical scenarios for children. While systolic dysfunction and pericardial effusion are the most common indications for performing cardiac POCUS, specific indications emerging in the pediatric heart disease and pediatric cardiac critical care settings include right ventricular failure and position evaluation for mechanical circulatory support devices. The latter are indications that would be applicable only to centers taking care of patients with advanced pulmonary hypertension or advanced heart failure and cardiogenic shock. Additionally, utilization of the cardiac POCUS is an evolving use and may be particularly helpful in elucidating shock states [26]. Figure 17.11 summarizes the approach to cardiac and lung POCUS evaluation of unexplained hemodynamic instability in the intraoperative or postoperative settings [1].

POCUS during assessment of shock

There are varying etiologies of shock (e.g., cardiogenic, hypovolemic, septic). POCUS, in addition to traditional methods for elucidating the type of shock, such as physical examination and hemodynamic parameters (e.g., cardiac output, heart rate, central venous pressure), can be tremendously helpful particularly for guiding fluid therapy and vasoactive medications. The surviving sepsis campaign international guidelines suggest the use of POCUS of advanced echocardiography in tailoring therapy for children with sepsis [27].

Hypotension or shock due to right ventricular failure

A patient with a clinical picture concerning for new pulmonary embolism – syncope, hypotension, ECG changes, and/or desaturation – may be a scenario for a cardiac POCUS while awaiting laboratory results. The presence of severely depressed right ventricular function may suggest right ventricular failure due to an embolic event. The right ventricular systolic function can be assessed in the PLAX, PSAX, and apical four-chamber views. Final diagnostic studies with echocardiogram and chest computed tomography (CT) scan are still needed; however, a cardiac POCUS performed by a credentialed team that shows these findings may be a criterion for activating surgical and/or mechanical support teams.

A patient with underlying pulmonary hypertension (idiopathic, genetic, or secondary to CHD) may present with signs and symptoms concerning for episodes of right ventricular failure, e.g., worsening hypotension, ST segment changes, and/or desaturations. An assessment of the position of the interventricular septum on cardiac POCUS can yield important clues to the best next step for management. Diagnosis of worsening pulmonary hypertension by POCUS can lead to the early initiation of additional or new pulmonary vasodilators. Additionally, a septum bowing into the left ventricle with preserved left ventricular function suggests that vasoconstrictor agents (vasopressin or norepinephrine) may be beneficial to increase the left ventricular afterload to optimize ventriculo-ventricular interactions by shifting the interventricular septum over toward the right ventricle and into a more neutral position. This can permit better left ventricular preload and function to improve cardiac output. This assessment is best performed in the PSAX view to assess the interventricular septum as well as the relative left and right ventricular sizes.

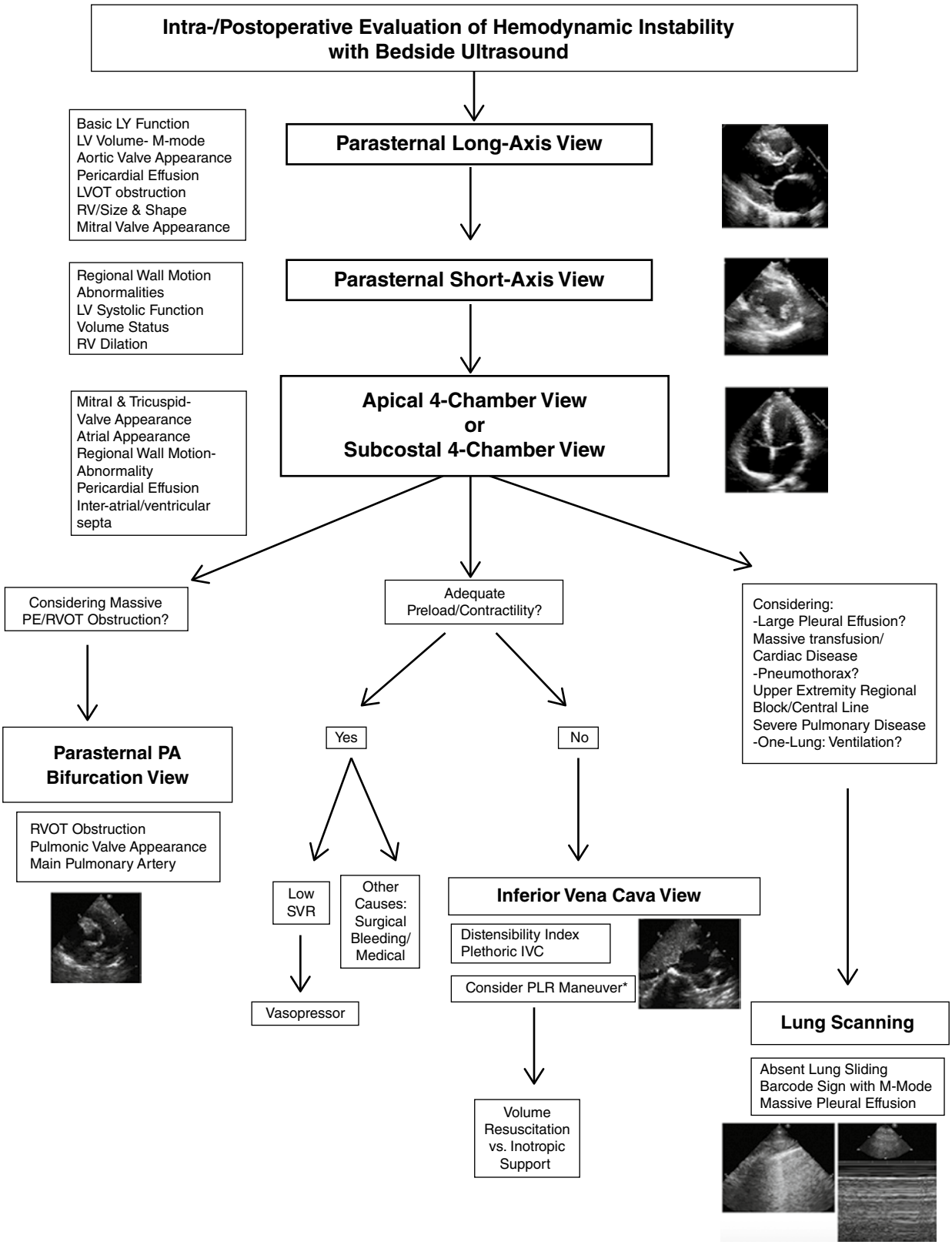


Figure 17.11 Perioperative anesthesia ultrasound evaluation approach for intraoperative/postoperative bedside ultrasonography during unexplained periods of hemodynamic instability. LV, left ventricle; PE, pulmonary embolism; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; PTX, pneumothorax; PA, pulmonary artery; SVR, systemic vascular resistance; IVC, inferior vena cava; PLR, passive leg raise. (Source: Adler et al. [1]. Reproduced with permission from Elsevier.)

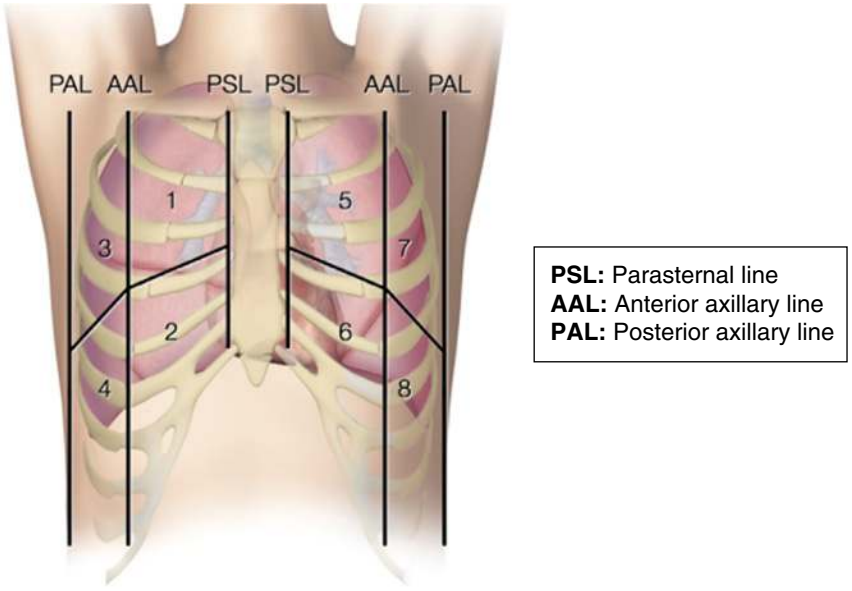


Figure 17.12 Diagram indicating suggested scan planes for lung point-of-care ultrasound. (Source: Diaz-Gomez et al. [30]. Reproduced with permission from Elsevier.)

Position of cannulae or device for patients on mechanical support

An evolving use of cardiac POCUS is the assessment of position of mechanical circulatory support devices; particularly, the positioning of venous cannula in venous-arterial extracorporeal membrane oxygenation (ECMO) cannulation or the dual-lumen cannula (e.g., Avalon cannula) is utilized for venovenous ECMO cannulation [28]. At the time of initial cannulation, the positioning of the venous cannula, particularly for venovenous ECMO, is typically performed under formal echocardiogram guidance [29]. However, if there is an urgent change in oxygen saturations or concern for worsening recirculation, cardiac POCUS in the subcostal views can be utilized by credentialed operators to assess the position of the outflow and inflow ports. When a dual-lumen cannula is utilized for venovenous cannulation, the tip of the cannula is positioned in the IVC with the outflow port in the superior one-third of the right atrium with flow directed toward the tricuspid valve.

The Impella® device is increasingly used for mechanical support in pediatric patients in cardiogenic shock. The positioning of the Impella® requires device-specific distance between the aortic valve and the tip of the device as well as between the mitral valve and the device. Repositioning of the device may be needed in case of any movement or migration, as malposition can cause suction events, inadequate support, or worsening hemolysis. Although not yet well investigated in pediatrics, a cardiac POCUS may be helpful in these situations to help reposition the device with the assistance of the interventional cardiologist. The most useful views for this purpose would be a PLAX view as well as the apical four-chamber view, to evaluate the device in the long axis.

It is important to note that these device-specific uses of cardiac POCUS require technical knowledge of the technology being evaluated. This is ideally suited to institutions with formal cardiac POCUS protocols for these specific indications as well as cohorting of these technologies, patients, and their providers. This will allow the relevant operators to be familiar with the appropriate positioning of the mechanical support devices as well as allow them case volumes to maintain competence of their skills in performing these assessments.

Performing lung POCUS

Basic lung POCUS relies on scanning of two to three planes and is generally performed while the patient is supine. The chest can be divided into segments to ensure that the provider scans all portions of the chest. The provider should scan long the anterior and posterior axillary lines and along the parasternal line (Figure 17.12) [30]. Scanning of these planes ensures that all lung segments are evaluated in a brief but systematic way. Similar to all diagnostic modalities, lung ultrasound is operator dependent and requires deliberate training to ensure that the sonographer is able to recognize the ultrasonographic signs indicative of pathology.

Scanning is performed using the linear array probe with the orientation marker in the 12 o′ clock position and should proceed systematically (Figure 17.13) [31].

Structures by artifact visualization

A-lines
- Motionless artifacts that are reverberation reflections of the pleural line
- Appear at repeated and fixed intervals from the pleural line (Figure 17.14)
- Normal finding in the presence of pleural sliding (Figure 17.15)

B-lines
- Hyperechoic laser-like projections extending from the pleural line to the bottom of the screen (Figure 17.15)
- Typically obliterate A-lines
- Usually indicative of increased lung parenchymal density as seen with pulmonary edema



Figure 17.13 Probe positioning for lung ultrasound in the parasternal line (A) and posterior axillary line (B). Red dot indicates location of orientation marker. (Source: Adler et al. [1]. Reproduced with permission from Elsevier.)

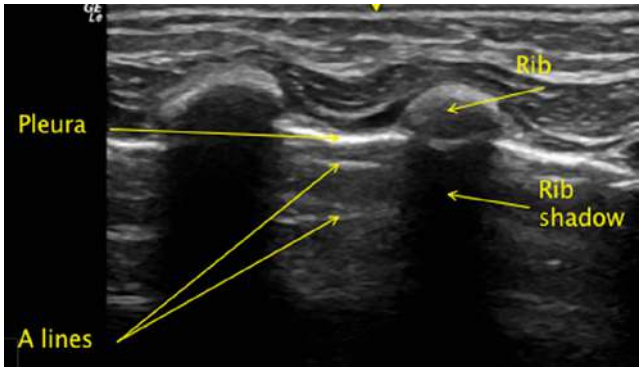


Figure 17.14 Lung ultrasound imaging demonstrating the appearance and location of the pleural line, ribs, and ensuing shadowing as well as A-line reflections of the pleural line.

Lung Sliding	• Shimmering motion artifact representing normal movement of the opposing visceral and parietal pleura during the respiratory cycle
Seashore Sign	• Granular and homogenous pattern visualized on M-mode below the pleural line (Figure 17.16) • Normal finding indicative of the interface between the chest wall and the mobile lung
Barcode Sign	• Sonographic sign of absent lung sliding using M-Mode (Figure 17.16) • Change in appearance from a Seashore to a Barcode appearance below the pleural line • Pathognomonic for pneumothorax
Spine Sign	• Visualization of the thoracic vertebral bodies • Indicative of fluid (effusion, hemothorax, and consolidation) enhancing the ultrasound waves allowing for deeper penetration to visualize the spine
Lung Point	• Distinct area of transition between normal lung sliding and absent lung sliding • Pathognomonic for pneumothorax
Lung Pulse	• intermittent pulsation of the pleural line (without lung sliding) synchronous with the heartbeat • Occur with increased lung density (atelectasis) or in the absence of ventilation (without pneumothorax) such as during contralateral one lung ventilation

Performance of lung ultrasound should occur systematically across all regions of the chest with the intent on observing specific sonographic signs above to identify normal lung from pathology [30] (Figure 17.17).

Incorporation of lung ultrasound into anesthesia practice

The majority of reports using lung ultrasound perioperatively has been limited to case reports and series [32–34]. While lung ultrasound can be useful in identifying etiologies for pulmonary-related issues, it is likely that the fully utility of this modality has yet to be realized within anesthesia practice. Lung ultrasound has been successful in guiding airway management, particularly the assessment of one lung ventilation [35, 36]. Additionally, lung ultrasound has been shown to assist ventilatory management in patients undergoing congenital heart surgery. Song et al. performed a randomized controlled study using ultrasound guided lung recruitment to rescue intra and postoperative desaturation as well as mechanically ventilatory times in children undergoing congenital heart surgery [37].

Comparative analysis conducted by Wu et al. assessed the diagnostic ability of perioperative lung ultrasound for identification of excessive pulmonary blood flow (detection of

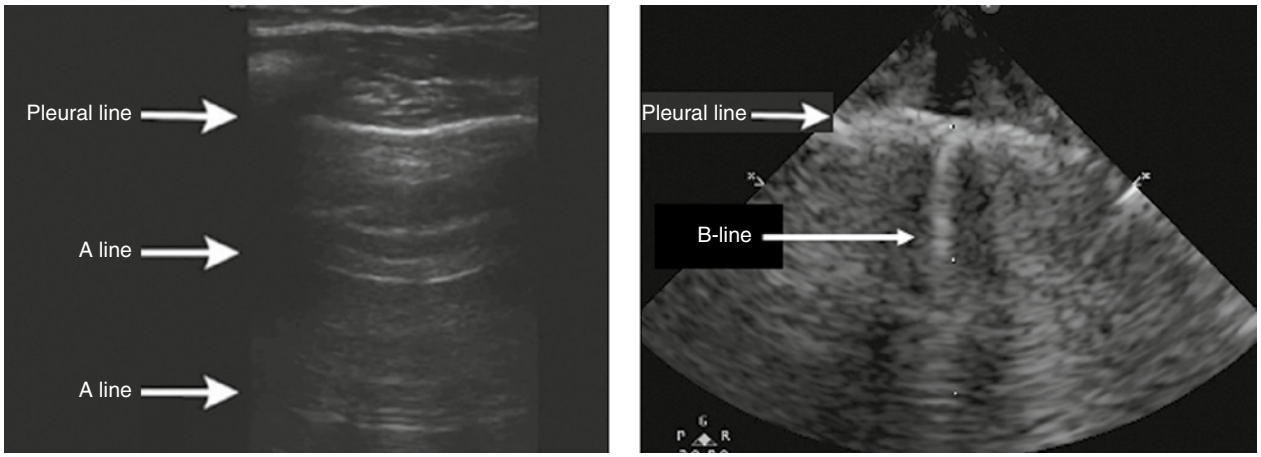


Figure 17.15 Lung point-of-care ultrasound demonstrating the presence of the pleural line and A-lines (left panel) and B-lines (right panel)

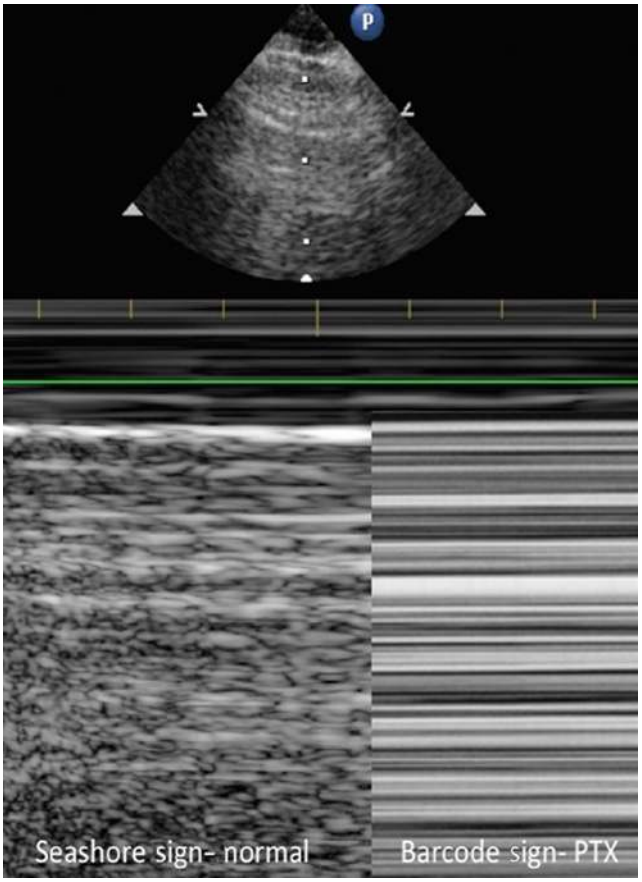


Figure 17.16 Lung point-of-care ultrasound (Motion Mode: M-Mode) demonstrating the change of appearance from normal aerated lung (left) with a seashore sign to appearance with presence of a pneumothorax (PTX-right) and a barcode sign. (Source: Adler et al. [1]. Reproduced with permission from Elsevier.)

pleural fluid and pulmonary edema as indicated by B-lines) as often seen in children with CHD [38]. Specifically, they evaluated the diagnostic abilities of lung ultrasound in comparison with preoperative chest X-ray (CXR) and CT [38]. This study demonstrated the sensitivity and specificity of lung ultrasound (96 and 95%, respectively) to be similar to chest CT and far superior to CXR (74 and 50%, respectively) for the detection of excessive pulmonary blood flow and interstitial edema [38].

POCUS training and credentialing

Again, while POCUS specific machines have fewer controls and cardiac POCUS imaging protocols are simpler than standard echocardiography, cardiac imaging remains a complex task and one should not believe that cardiac POCUS training is a simple endeavor. Short weekend or day-long POCUS crash courses or workshops may be able to provide some fundamental knowledge to begin POCUS training. However, experts consistently recommend that the best approach to teach POCUS is multifaceted, including longitudinal training programs which emphasize and demonstrate learner competency [8, 39, 40]. Published pediatric POCUS training programs tend to be multidisciplinary in nature, drawing upon expertise of subspecialists in order to cover the POCUS imaging cores [11, 23, 41]. For cardiac POCUS, collaboration with cardiology subspecialists and the institutional echocardiography laboratory provides invaluable access to expert operators and cardiac pathology exposure [23, 42].

The basic cardiac POCUS curriculum components typically include didactics, cardiac ultrasound image library, and supervised hands-on scanning; ultrasound simulators or cardiac phantoms may also be used to complement patient scanning experiences [8]. Dedicated faculty with interest in cardiac POCUS and education is needed to create the didactics and image library or to curate free online medical education materials. Faculty mentorship for learner bedside scanning supervision or remote image review is critical, but this is more time-consuming and can be challenging to maintain.

Didactics for cardiac POCUS should include fundamentals of ultrasound physics, including artifacts and the fundamentals of machine use. Typically, this also includes instruction of terminology and basic probe orientation. While there are fewer options for image optimization and probe

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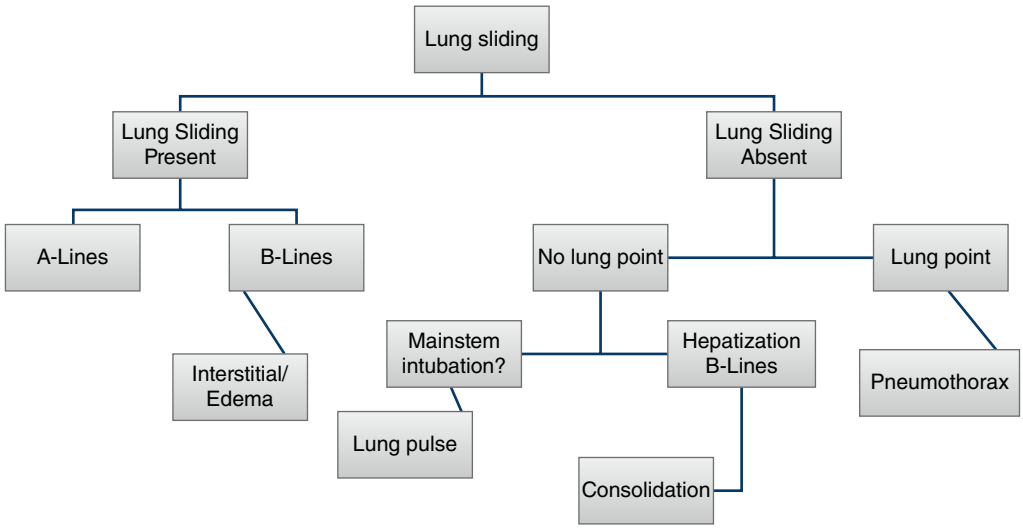


Figure 17.17 Suggested algorithm for approaching lung point of ultrasound for the anesthesia provider.

selection with POCUS machines to review, the imaging limitations of these machines compared to standard echocardiography should be emphasized. Additionally, the scope of practice of cardiac POCUS as compared to standard echocardiography should be reviewed, particularly related to the limited diagnostic targets in POCUS and the concerns regarding its use in CHD [14]. Optimal method or modality of didactics is not established, but asynchronous or online methods can be an attractive solution to teach medical personnel with busy clinical schedules. Additionally, online teaching can be viewed repeatedly by users and potentially provide the opportunity for a learning forum for discussion or interactivity with other learners and experts [43].

Development of competent cardiac POCUS psychomotor skills requires a component of hands-on training, of which at least some should be directly proctored by an expert user [8, 44]. This can be accomplished in different manners, including dedicated standardized patient workshops or in clinical scenarios with a mentor. Weekend workshops provide opportunities for scanning on multiple standardized patients with variable quality of imaging windows. If designed well, the workshop should have ample time for expert feedback on the technical aspects of imaging acquisition. However, given the nature of standardized patients or volunteers, there will likely be a paucity of pathology. Proctored scanning in clinical scenarios can provide opportunities for pathology exposure, but caution is recommended regarding clinical integration of learner scan findings. This can be ameliorated by the usage of clear terminology (POCUS vs. standard echocardiography) and proctors aware of the clinical scenario as well as the scope of practice for POCUS and standard echocardiography.

In pediatric centers, even large ones, cardiac pathology can be relatively rare and exposing a number of POCUS learners to enough pathology in clinical scenarios in a finite period of time can be difficult. POCUS image libraries can provide avenues to improve learners' competency to recognize cardiac disease, particularly recognizing the variety of ventricular systolic dysfunction [23]. Again, there are multiple free online medical education resources (mostly adult medicine centric) to draw from. These image libraries can also be created locally drawn from institutional POCUS and standard echocardiography images (http://learn.pocustraining.com). These libraries can also be used track users' progress and provide feedback (individually or via expert comments on specific POCUS images).

Teaching POCUS with a goal of competency is the optimal approach and it can provide a pathway for a local credentialing process. Assessment of cardiac POCUS competency is an evolving science but seems to be based on a combination of number of scans performed and an expert assessment of the quality of the acquired images. Conlon et al published that a minimum of 25 certified cardiac POCUS scans as the criteria for credentialing purposes in their pediatric critical care medicine division [11]. Mechanisms for expert feedback on adequacy and quality images are important for credentialing, but also for ongoing quality assurance programs. Some POCUS imaging reporting systems provide quality assurance packages. There are also available cardiac POCUS assessment tools available to provide richer feedback for both teaching and ongoing quality assurances purposes [45]. Cardiology consultation is likely helpful to build and maintain cardiac POCUS credentialing and quality assurance processes, but both the American Medical Association and American Council of Emergency Physicians recommend that credentialing processes remain internal within the subspecialty [46, 47]. This recommendation is likely due, in part, that POCUS scope of practice within a subspecialty is best ultimately determined by the subspecialists themselves.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

1 Adler AC, Greeley WJ, Conlin F, Feldman JM. Perioperative anesthesiology ultrasonographic evaluation (PAUSE): a guided approach to perioperative bedside ultrasound. J Cardiothorac Vasc Anesth 2016;30:521–9. An early review of POCUS in anesthesiology with well-organized flowcharts for preoperative, and intra/postoperative assessment of abnormal hemodynamic states using a differential diagnosis approach.

3 Narula J, Chandrashekhar Y, Braunwald E. Time to add a fifth pillar to bedside physical examination: inspection, palpation, percussion, auscultation, and insonation. JAMA Cardiol 2018;3:346–50. A well-written review arguing that bedside ultrasound techniques, including cardiac POCUS, lead to more accurate diagnoses than physical examination alone. The significant advances in miniaturizing the bedside technology are also presented.

5 Kimura BJ. What is an echo machine? J Am Soc Echocardiogr 2010;23:1238–41. An interesting opinion piece warning that the disruptive technology and wide availability of bedside echocardiography may come at the cost of resolution and accuracy of imaging, and emphasizing the limitations of POCUS for cardiac imaging.

14 Singh Y, Tissot C, Fraga MV, et al. International evidence-based guidelines on point of care ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Crit Care 2020;24:65. A comprehensive review of the evidence, and the recommendations for use of POCUS in neonates and children, along with levels of evidence for cardiac, lung, and other modalities. A total of 41 clinical scenarios is evaluated; about half were deemed to have quality of evidence rated A or B on an A through D scale.

24 Adler AC. Perioperative point-of-care ultrasound in pediatric anesthesiology: a case series highlighting intraoperative diagnosis of hemodynamic instability and alteration of management. J Cardiothorac Vasc Anesth 2018;32:1411–4. A case series including air embolus, pleural effusion, pericardial tamponade, and ventricular dysfunction, which has well-defined images of each scenario as well as on line supplementary material with the corresponding videos.

28 Bautista-Rodriguez C, Sanchez-de-Toledo J, Da Cruz EM. The role of echocardiography in neonates and pediatric patients on extracorporeal membrane oxygenation. Front Pediatr 2018;6:297. A well-written review of POCUS for ECMO in neonatal and pediatric patients, including cannula position, pericardial tamponade, intracardiac thrombus, and ventricular dysfunction. Includes figures with examples of all of these clinical scenarios.

32 Adler AC, Matisoff AJ, DiNardo JA, Miller-Hance WC. Point-of-care ultrasound in pediatric anesthesia: perioperative considerations. Curr Opin Anaesthesiol 2020;33:343–53. An up to date summary of POCUS in pediatric anesthesia; includes a review of cardiac, lung, airway, and gastric ultrasound, along with their limitations.

37 Song IK, Kim EH, Lee JH, et al. Utility of perioperative lung ultrasound in pediatric cardiac surgery: a randomized controlled trial. Anesthesiology 2018;128:718–27. A randomized controlled study using ultrasound guided lung recruitment to rescue intra and postoperative desaturation as well as mechanically ventilatory times in children undergoing congenital heart surgery. Lung POCUS was effective in improving atelectasis and oxygenation, and reduced time on mechanical ventilation compared to standard therapy.

39 Fagley RE, Haney MF, Beraud AS, et al. Critical care basic ultrasound learning goals for American Anesthesiology Critical Care Trainees: recommendations from an Expert Group. Anesth Analg 2015;120:1041–53. Recommendations from a group of experts emphasizing that the best approach to teach POCUS is multifaceted, including longitudinal training programs which emphasize and demonstrate learner competency over time; rather than short training courses.

42 Kirkpatrick JN, Grimm R, Johri AM, et al. Recommendations for echocardiography laboratories participating in cardiac point of care cardiac ultrasound (POCUS) and critical care echocardiography training: report from the American Society of Echocardiography. J Am Soc Echocardiogr 2020;33:409–22.e4. Recommendation for training in cardiac POCUS, which include collaboration with cardiology subspecialists and the institutional echocardiography laboratory, which provides invaluable access to expert operators and cardiac pathology exposure.

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CHAPTER 18
Preoperative Evaluation and Preparation

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Introduction

Congenital heart defects (CHD) are the most common of all congenital anomalies. Every day in the United States, 11,500 babies are born; of whom 450 have a congenital anomaly, of which 87 (20%) are congenital heart defects [1]. The incidence of CHD has remained consistent over the years and is similar across various geographic, racial, and ethnic groups. Although there is a suggested increase in the prevalence of specific lesions in certain regions, the incidence is mostly 7–10/1,000 live births [2, 3].

The patient with congenital heart disease

The demographics of patients with CHD are changing as screening methods evolve, diagnostic tools improve, and interventions change. Although CHD is frequently considered a disease of childhood, the population of adults with CHD is growing at the rate of 5% every year, and by the end of this decade, there will be more adults than children with CHD. The congenital cardiac anesthesiologist thus must be prepared to evaluate and care for adults as well as children with heart defects. However, there remains a significant population of neonates and infants with critical CHD who require care in their first days or months of life. In an epidemiologic study, 15% of all infants with CHD had significant physiological compromise (metabolic acidosis, seizures, cardiac arrest, or evidence of renal or hepatic injury) that required an invasive intervention in the first few weeks of life [4]. Many lesions are diagnosed prenatally, and fetal interventions to improve the outcome and progress of patients are increasingly applied [5]. The interventions are also changing rapidly, and an anesthesiologist must include in the preoperative evaluation an understanding of the planned procedure, the location, and the coordination needed between various teams. Many centers have adopted a hybrid approach to many defects, especially hypoplastic left heart syndrome [HLHS]) and multiple ventricular septal defects (VSDs). These procedures will require an up-to-date understanding and preparation for those ever-changing interventions [6, 7].

Terminology and classification

The primary step in the preoperative anesthetic evaluation of the patient with CHD is an understanding of the terminology and nomenclature used for these defects. The communication between various chambers and vessels is described in terms

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of concordance and/or discordance. Sidedness and morphology of chambers, valves, and vessels also follow a standard description approach. To understand the nomenclature of a specific lesion, the anesthesiologist carefully considers:

- Systemic and pulmonary venous drainage
- The outlet/drainage of the atrial and ventricular chambers (e.g., a double inlet left ventricle [DILV] has both right and left atria draining into the left ventricular chamber; in a double outlet right ventricle [DORV] the right ventricle communicates directly to both the systemic and pulmonary outlets)
- Atrioventricular and ventriculoarterial communication (e.g., in congenitally corrected transposition of the great arteries [CCTGA] there is atrioventricular and ventriculoarterial discordance)
- The morphology of the atrioventricular and semilunar valves Systemic and pulmonary arterial morphology and branching.

Following an interpretation of the nomenclature and terminology, the anesthesiologist has to understand the physiologic implications of various lesions. The most practical approach is to follow a physiologic classification for all CHDs (Table 18.1). Many CHDs that present in the neonatal period requiring urgent care are ductal-dependent lesions where a patent ductus arteriosus is essential to maintain either systemic or pulmonary flow. Defects presenting later in life or requiring later care are classified according to the presence and direction of shunting, pulmonary blood flow, and obstruction. Although there are numerous CHDs, the majority will be classified into one of four categories, with the incidence of the most commonly seen defects representing one of each of those categories [8, 9]. Chapter 4 has a detailed presentation of the terminology and nomenclature of different CHDs.

Table 18.1 Classification of congenital heart defects

Category	Shunt direction	PBF	Most common examples
Ductal-dependent lesions (neonatal period)			
DDL for PBF	L-to-R	Decreased	Pulmonary atresia, tricuspid atresia, TOF with severe PS, Critical PS
DDL for SBF	R-to-L	Increased	HLHS, Preductal coarctation, IAA, Critical AS
Common CHD			
Acyanotic shunt lesions	L-to-R	Increased	**VSD** (**20%**), ASD (16%), PDA (12%), P/CAVC (4%)
Cyanotic shunt lesions	R-to-L	Decreased	**TOF** (**7%**), Ebstein anomaly, PA-VSD-MAPCA
Obstructive lesions	No shunting	Normal	**Coarctation** (**6.8%**), AS, PS, cor triatriatum, MS
Mixing lesions	L ↔ R	Variable	**d-TGA** (**3.6%**), Truncus Arteriosus, TAPVR
Regurgitant lesions	No shunting	Normal	MR, TR, AI, PI (most post-surgical repairs)
Others	Variable shunting	Variable	Vascular rings, anomalous coronary lesions (ALCAPA), tumors, cardiomyopathy (IDCM, HCM)

DDL, ductal-dependent lesion; PBF, pulmonary blood flow; L, R, left and right; TOF, tetralogy of Fallot; PS, pulmonary stenosis; SBF, systemic blood flow; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; AS, aortic stenosis; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; P/CAVC, partial or complete atrioventricular canal defect; PA-VSD-MAPCA, pulmonary atresia with a ventricular septal defect and multiple aortopulmonary collaterals; MS, mitral stenosis; d-TGA, dextro-transposition of the great arteries; TAPVR, total anomalous pulmonary venous return; MR, mitral regurgitation; TR, tricuspid regurgitation; AI, aortic insufficiency; PI, pulmonary insufficiency; ALCAPA, Anomalous origin of the left coronary artery from the pulmonary artery; IDCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

Multidisciplinary approach

The preoperative period is the appropriate time to consider all the variables that can impact the preparation, planning, and conduct of the perioperative care for the child with CHD. The majority of congenital cardiac centers have a set weekly conference to discuss patients scheduled for surgical as well as catheter interventions. In that multidisciplinary conference, the history and condition of the patients are discussed, imaging studies are reviewed, and plans for any further consults or tests are investigated. The goal of the conference and the preoperative evaluation is to bring all the necessary expertise to understand the lesion, optimize the condition of the patient, and plan the best approach or intervention to the patient.

Consent

The preoperative visit is an essential phase in preparing children with CHD and their families for the upcoming intervention. Parental knowledge, whether provided verbally or in written or visual form has been shown to improve the parents' involvement and effectively reduce their anxiety [10]. The purpose of the preoperative visit and the consent process is not the delivery of information and significant potential risks, but to provide the necessary knowledge to the parents (and potentially the child) of the specifics of the anesthetic procedures, the common risks and the plans to prevent or mitigate them, and the role of the various caregivers. The consent process should bring the physicians and the family together as partners with the same purpose: the best care possible and the least risk acceptable for the care of the child. Well-informed parents are able to participate in educating their children and preparing them for the intervention through therapeutic play interventions, establishing a rapport and connection with the anesthesiologist. Children whose parents are better educated and informed, and who are involved in the preparation process are less anxious and more prepared for the interventions [11].

KEY POINTS: APPROACH IN PATIENTS WITH CHD

- CHD is the most common birth defect requiring intervention, and survivors have increasingly complex CHD.

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- Venous drainage, outlets of atria and ventricles, atrioventricular and ventriculoarterial communication, the morphology of the cardiac valves, and arterial branching are crucial components of classification and nomenclature of CHD.
- A multidisciplinary planning conference for surgical patients that includes surgeons, anesthesiologists, cardiologists, intensivists, and radiologists is a key component of the perioperative care of the patient with CHD.

Preoperative evaluation

History and physical examination

An initial pre-anesthetic evaluation includes reviewing accessible medical records, ordering appropriate preoperative tests, requesting appropriate consultations, and performing a thorough history and physical examination. Although most children have undergone a thorough evaluation by their pediatric cardiologist and cardiac surgeon, the history should not only address cardiopulmonary reserve but also other multisystem co-morbidities that may affect anesthetic management. A review of the child's medical record should assess the child's underlying congenital heart pathology and whether that pathology is repaired or palliated; previous surgery, anesthetic experiences and complications, and diagnostic and therapeutic interventions; current medications and medication history; and drug or food allergies.

A child's functional status will reveal information about their cardiopulmonary reserve. Functional status is assessed differently at different ages. Feeding difficulties with associated tachypnea, dyspnea, and diaphoresis with subsequent growth abnormalities and frequent pulmonary infections indicate limited cardiopulmonary reserve in the neonate and infant. School-aged children may exhibit decreased activity level or exercise intolerance with an inability to keep up with their peers, whereas older children may not only display fatigue, dyspnea, and orthopnea but may also verbalize chest pain, palpitations, and pre-syncope or syncope. Furthermore, recent changes in baseline activity indicate a further decline in cardiopulmonary reserve.

Recent upper (URI, upper respiratory infections) and lower respiratory tract infections (RTI) should be noted, as both may affect airway reactivity for 2–8 weeks [12]. RTI may additionally affect pulmonary vascular resistance (PVR), which may be poorly tolerated in those children with bidirectional cavopulmonary anastomosis (Glenn procedure), total cavopulmonary anastomosis (Fontan), underlying pathology, shunt physiology, or pulmonary vascular disease. The increased risk of breath-holding, airway obstruction, and laryngospasm with subsequent changes in ventilation and oxygenation poses an increased risk to children with limited cardiopulmonary reserve.

The recent COVID-19 pandemic has heightened our awareness of the potential risk of proceeding with elective procedures in the face of a URI, even in asymptomatic patients, and the need to protect healthcare providers as well as other patients when planning unavoidable procedures on such patients [13]. Even in the asymptomatic SARS-COVID-19 polymerase-chain-reaction (PCR) positive patient, the incidence and degree of respiratory complications are higher than in children with other UTIs. Careful screening, identification of at risk-patient, selective scheduling, and safe practice with protective personal equipment for the care providers are essential lessons learned from this pandemic that will be applicable and useful for any future similar viral pandemics [14].

Laboratory tests are available to potentially confirm the diagnosis of an RTI. Nasopharyngeal swabs or aspirates may detect common viral infections, but, depending on the phase of the infection, they may offer limited sensitivity. White blood cell counts are a poor indicator of infection, especially in neonates and children with immature or impaired immune systems. Chest radiograph findings typically lag behind the presentation of clinical symptoms in children with lower RTIs and are often of little utility. Children with URIs undergoing cardiac surgery have an increased incidence of postoperative complications when compared with children without a URI. The recommended period for recovery from a URI and avoiding perioperative respiratory adverse events is a 4- to 6-week period for the recovery of mucosal and ciliary function in children scheduled for cardiac surgery or catheterization, especially if airway instrumentation is planned [15, 16]. Children with underlying congestive heart failure (CHF) who present with a URI pose a dilemma for the perioperative team. It may be challenging to distinguish baseline CHF symptoms as noted earlier from URI symptoms. Furthermore, although decreased respiratory reserve in children with a respiratory tract infection may place the child at risk for perioperative complications, the need for surgical expediency given the CHF may obviate the URI symptoms, and it may be prudent to proceed with surgery to prevent further progression of the CHF.

The physical examination further assesses the child's general condition. Observation of the child during the pre-anesthetic evaluation may be the most valuable component of the physical examination. Is the child active, playful, age-appropriate, lethargic, or in failure to thrive compared with similarly aged children? Vital signs, including weight and height, heart rate, respiratory rate, blood pressure, and oxygen saturation (SpO_2) should be recorded. Failure to thrive with reduced weight and height indicates limited cardiopulmonary reserve and functional status. Blood pressure variation between extremities suggests an unexpected coarctation of the aorta. Tachypnea is one of the earliest signs of CHF. Cyanosis is usually recognized when the SpO_2 is 85% or lower and is associated with unrepaired or palliated CHD from decreased pulmonary blood flow and right-to-left shunting, but children with left-to-right shunting may also have desaturation from pulmonary edema [17]. Progressive cyanosis or frequent cyanotic episodes suggest the potential for rapid cardiopulmonary decompensation intraoperatively. Pre-ductal and post-ductal oxygen saturations should be recorded in an infant with an unrepaired defect. If the pre-ductal (right arm) saturation is higher than the post-ductal saturation, deoxygenated blood from the pulmonary circulation enters the descending aorta through a patent ductus arteriosus (PDA). This differential cyanosis may occur with persistent pulmonary hypertension of the newborn and left-heart abnormalities, such as

aortic arch hypoplasia, interrupted aortic arch, critical coarctation of the aorta, and critical aortic stenosis.

The remainder of the physical examination should be a detailed evaluation of the airway, chest, and heart, with any changes from baseline noted. Wheezing and rales on lung auscultation indicate not only reactive airway disease, chronic lung disease, or an acute pulmonary infection but also CHF. Auscultation of the heart should ideally be performed in a quiet setting with the child being calm and cooperative. Heart sounds, pathologic murmurs, particularly a different murmur from previously documented, gallop rhythms, and the presence of a thrill representing a palpable murmur should be noted. Hepatomegaly, jugular venous distension, and peripheral edema indicate CHF, from either left- or right-sided pathology. Jugular venous distension is of limited value in neonates and infants but may provide qualitative information about central venous pressure in older children [18]. Heart sounds and murmurs are influenced by patient position during auscultation as well as the period of the respiratory cycle during which the heart sound or murmur is being evaluated. Repositioning the child from supine to sitting decreases venous return suddenly and improves the auscultation of heart sounds and murmurs. Innocent murmurs increase in intensity in the supine position. Diminished peripheral pulses and delayed capillary refill indicate reduced systemic perfusion. The peripheral pulse will be reduced in the arm in which the subclavian artery to pulmonary artery shunt (Blalock–Taussig shunt) was constructed; the blood pressure will also be reduced in that ipsilateral arm. Finally, clubbing may indicate long-standing cyanosis. New or different physical examination findings from baseline necessitate further evaluation, which may include a chest radiograph, electrocardiogram (ECG), or echocardiogram.

Current and potential vascular access sites should be assessed, as it is frequently difficult to obtain access in children with CHD. Parents often have insight and knowledge about previous vascular access that can facilitate the selection of sites for potential vascular access. Children with CHD often have multiple previous arterial and venous cannulations that may result in trauma or thrombosis to those vessels. That information is additionally valuable when considering what potential sites to access. Arterial access should be avoided on the side where a Blalock–Taussig shunt was constructed as peripheral pulses and blood pressure will be reduced in that ipsilateral arm.

The airway evaluation is an essential component of the preoperative evaluation of children with CHD, particularly those with chromosomal abnormalities and syndromes. Airway evaluation should include a history of noisy breathing that may indicate airway compression from supraglottic or subglottic obstruction; for example, children with aortic arch obstruction have a 27% incidence of subglottic airway compression that becomes more symptomatic postoperatively following an end-to-side aortic arch reconstruction [19]. Previous airway history also includes previous airway interventions and complications and previous surgery to the face and neck. Airway physical examination includes assessing body mass index, patency of nares, degree of mouth opening, tongue size, palate shape and size, mandibular size, and neck mobility. Mandibular size with micrognathia and retrognathia is associated with difficult mask ventilation and intubation [20]. Many chromosomal abnormalities and syndromes that are associated with CHD, including trisomy 13, 18, and 21, DiGeorge syndrome and Turner syndrome, have an abnormal airway examination that may indicate possible difficult mask ventilation or intubation. Patients with conotruncal abnormalities, including pulmonary atresia, truncus arteriosus, and interrupted aortic arch are at increased risk for DiGeorge syndrome or velocardiofacial syndrome (partial deletion of chromosome 22q11.2). All neonates and infants with reduced functional residual capacity and increased oxygen consumption require a patent airway to prevent cardiorespiratory decompensation, but children with cyanotic CHD or pulmonary vascular disease are particularly at risk of inadequate ventilation and oxygenation from a compromised airway. Previous anesthetic records should always be reviewed for any potential difficulty in mask ventilation and/or intubation along with any airway adjuncts used during mask ventilation, intubation, or extubation.

Children with trisomy 21 frequently present for surgical and other interventions at various stages of life. As these children's age progresses, the risk of hypotonia, atlanto-axial instability, and spinal cord compression increases [21]. Many centers have adopted an algorithm to approach these patients and decide on the imaging needed and the best approach to the airway [22]. The algorithm applies standard cervical spine series with flexion and extension views in older trisomy 21 patients, or patients with any signs or symptoms of atlanto-axial instability. An atlanto-dens interval >4.5 mm or a neural canal width <14 mm provides indirect evidence of cervical spine instability and will require confirmation by magnetic resonance imaging (MRI). If confirmed, these findings in the preoperative period are significant for a high risk of atlanto-axial instability and the need for a neurosurgical consult, potential surgical fusion, or, at a minimum, a modification of airway management and intraoperative positioning.

The finding of poor laryngoscopic view, reported as a Cormack and Lehane [23] grade III or IV, is significantly higher in children with CHD, with a reported incidence of 3.5%, twice as high as the general pediatric population. This incidence was higher in patients below 1 year of age (5.6%) and in those with concomitant chromosomal and genetic abnormalities [24].

Approximately 25–40% of children with CHD may have associated anomalies, which may include neurologic, airway, gastrointestinal, hematologic, endocrine, syndrome, or chromosomal abnormalities [25]. Approximately 5–10% of children with CHD have a known chromosomal abnormality – the most common abnormalities associated with congenital heart disease are listed in Table 18.2. (see Chapter 8 for further discussion of genetic syndromes and CHD).

Congestive heart failure

Similar to adults, children can have significant cardiac decompensation, resulting in poor peripheral perfusion and the inability to adequately support vital organ function. Unlike adults, where CHF is most commonly caused by myocardial ischemia and dysfunction, children may have CHF despite normal myocardial vascularity and function.

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Table 18.2 Chromosomal and genetic defects, syndromes and congenital heart disease

Chromosome, genetic, or phenotypic abnormality	Incidence	Associated CHD	Extracardiac anomalies
		Common chromosomal defects	
Trisomy 21 (Down syndrome)	1 : 650	CAVC, primum ASD, VSD	Mid-facial and mandibular hypoplasia, micrognathia, macroglossia, epicanthal folds, simian creases, pronounced hypotonia, atlanto-axial subluxation
Trisomy 13 (Patau syndrome)	1 : 7,500	VSD, PDA, BAV	Mid-facial hypoplasia, cleft lip, microphthalmia, microcephaly, developmental delay
Trisomy 18 (Edward syndrome)	1 : 7,000	Malalignment VSD, TOF, DORV	Prominent occiput, short neck, low set ears, small mandible, clenched fists
Monosomy X (XO-Turner syndrome)	1 : 2,500	BAV, AS, coarctation	Triangular facies with slanting palpebral fissure, short stature, webbed neck, difficult airway, lymphedema
22q11 deletion (DiGeorge–velocardiofacial syndrome)	1 : 4,000	Conotruncal anomalies, IAA, truncus arteriosus	Thymic hypoplasia, hypoparathyroidism, immunodeficiency, hypocalcemia, renal anomalies, learning disability
7q11 deletion spectrum (Williams syndrome	1 : 20,000	Valve and supravalvular AS, coronary ostial anomalies, peripheral PS	Elfin facies, friendly "cocktail" personality, developmental delay, short stature, hypercalcemia
		Common genetic defects	
Noonan syndrome (12q22 single gene defect)	1 : 2,000	HCM, PS, ASD, TOF, coarctation	Short webbed neck, micrognathia, dental malocclusion, cognitive delay, vertebral anomalies, pectus excavatum
Ehler–Danlos syndrome (variable gene mutation COL5A1)	1 : 5,000	AV/MV prolapse, aortic dissection	Temporomandibular joint dislocation, hyperextensibility of skin and joints, poor wound healing
Marfan syndrome (FBN1 single fibrillin gene defect)	1 : 5,000	Aortic root dilation/aneurysm, MVP	Airway abnormalities (high arched palate), pectus excavatum, scoliosis, joint dislocations
Duchenne muscular dystrophy (absent dystrophin gene Xp21)	1 : 3,500	Cardiomyopathy, conduction abnormality	Progressive respiratory failure, severe scoliosis, muscle wasting
		Syndromic Associations	
VACTERL	**V**ertebral, **A**nal, **C**ardiac (VSD, TOF), **T**racheoesophageal, **R**enal, and **L**imb defects		
CHARGE	**C**oloboma, **H**eart defect (TOF, Truncus), **C**hoanal atresia, **R**etardation, **G**enitourinary, **E**ar abnormalities		

CAVC, complete atrioventricular canal defect; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; BAV, bicuspid aortic valve; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; AS, aortic stenosis; IAA, interrupted aortic arch; PS, pulmonary stenosis; HCM, hypertrophic cardiomyopathy, AV, aortic valve; MV, mitral valve; MVP, mitral valve prolapse.

This may occur in the presence of significant volume overload (in shunt lesion) or pressure overload (in obstructive lesions), and frequently in patients with single-ventricular physiology, especially those with a systemic right ventricular morphology. CHF is characterized by reduced cardiac output and increased venous pressure in the systemic and/or pulmonary venous systems, often secondary to an abnormality in the myocardium. Cardiomyopathy is an abnormality of the myocardium. Cardiomyopathies are classified as dilated, restrictive, hypertrophic, arrhythmogenic, or unclassified [26]. Other causes of CHF in children include volume overload secondary to large left-to-right shunts, valvar regurgitation, and obstructive pathology. The classification of heart failure focuses primarily on the severity of illness. The New York Heart Association classification, which ranges from I (asymptomatic) to IV (heart failure with symptoms at rest), was designed for adults but may also be used for older children. The Ross Heart Classification Scale also ranges from I to IV but may be used in infants (see Table 18.3). Accurate assessment and grading of CHF in children require consideration of age, activity, and compensatory mechanisms. Thus the revised Ross Classification has five different age groups with the scaling system (0–2) evaluating different activities and findings per age group [27]. The Canadian Cardiovascular Society has established recent guidelines for the age-appropriate diagnosis of CHF, using commonly encountered symptoms, with recommendations for further investigations (brain natriuretic peptide [BNP], endomyocardial biopsy) and a stepwise introduction for medical therapy to optimize children with CHF prior to surgery and intervention [28].

The prevalence of heart failure-related hospitalization for children <18 years has not changed with time, amounting to 11,000–14,000 admissions annually. In a retrospective analysis of the largest pediatric admissions database, the Healthcare Cost and Utilization Project Kids' Inpatient Database, between 1997 and 2006, pediatric heart failure-related admissions were at the rate of 14.5–17.9/100,000 children. Although the prevalence has not changed significantly, the overall mortality is 7%, significantly higher than the overall expected mortality of 0.4% for all pediatric admissions with no, or compensated, heart disease. The hospital

Table 18.3 Ross classification of congestive heart failure in children

Stage	Presentation
A	Intact function but recognized to have a risk factor for the development of heart failure, e.g., exposure to cardiotoxic chemotherapy or a valvular abnormality that imposes a volume or pressure overload on the ventricle
B	Presymptomatic state where there is discernible myocardial dysfunction, including chamber enlargement or reduced systolic function. Never had signs or symptoms of heart failure
C	Present or past state of symptomatic heart failure. Includes patients with New York Heart Association (NYHA) class II and III disease as well as patients who have had signs or symptoms but are asymptomatic by virtue of heart failure treatment
D	Advanced heart failure requires specialized therapy such as intravenous inotropes or mechanical circulatory support

(Source: Ross [27]. Reproduced with the permission of Springer Nature.)

length of stay is significantly longer, and the outcome is clearly influenced by co-morbid conditions [29].

Children with limited cardiopulmonary reserve should be identified preoperatively as those children at the highest risk of perioperative morbidity and mortality. Preoperative evaluation should include the degree and progression of symptoms and heart failure therapy. The anesthesiologist should communicate directly with the treating cardiologist to assess the child's functional and clinical status. Additionally, strategies and decisions for escalation of care should be discussed with the child's parents, cardiologists, anesthesiologists, and/or intensivists. This might include the potential need for extracorporeal membrane oxygenation or other circulatory support devices. Infants with CHF often have difficulty feeding, diaphoresis with feeding, inadequate growth, and frequent pulmonary infections. Older children with CHF have symptoms similar to adults, including dyspnea at rest or exertion, orthopnea, angina, and peripheral edema. The clinical findings are similar to those seen in adults, with some variations specific to children. Common findings include tachycardia, shortness of breath, difficulty feeding, and lethargy. Hepatomegaly is frequently a characteristic sign of right-sided CHF, with edema seen in the sacral area (especially in babies) as well as the lower extremities. Left-sided CHF is manifested with pulmonary congestion, gallop on auscultation, and poor peripheral perfusion with cold and clammy skin. Children with CHF have low baseline blood pressure from the combination of diuretic therapy, angiotensin-converting enzyme (ACE) inhibitors, and beta-blocker therapy. Preoperative volume status should be assessed, as these children often have intravascular hypovolemia that is exacerbated by preoperative fasting. Children with CHF who are in-patients often have disease progression with increased perioperative risk. Those children who are treated with inotropes, vasodilators, and inodilators have the potential to deteriorate significantly with anesthetic exposure, and the ability to escalate support to maintain cardiac output is limited. B-type natriuretic peptide (BNP) is a hormone that is synthesized and released into the circulation by the ventricular myocytes in response to volume expansion and increases in myocardial wall stress. The marker is useful for assessing the functional status and cardiac function in those children with CHF. BNP is age- and gender-dependent, so higher BNP values are found in older female patients [30, 31]. Hypoxemia directly increases BNP production and is elevated in uncorrected or palliated single-ventricle patients.

Pulmonary arterial hypertension

Children with CHD and pulmonary hypertension (PAH) are at significant risk for perioperative cardiac complications, whether in the cardiac operating room, the catheterization laboratory or for non-cardiac procedures or imaging studies [32]. The preoperative assessment can be done using the clinical presentation, imaging studies, and, most importantly, cardiac catheterization information that reports the pulmonary/systemic pressure ratio and the reactivity of the pulmonary vascular bed [33]. Important information preoperatively is the response of the pulmonary vascular bed to oxygen, hyperventilation and inhaled nitric oxide and intravenous (IV) dilators. It is essential to consider the medical regimen for managing the patient, the potential benefit of additional therapy, and the safest interventions [34]. The preoperative use of single or combination therapy, including prostacyclin analogs (Treprostinil/Remodulin), endothelin receptor antagonists (Bosentan), and phosphodiesterase inhibitors (Sildenafil) even for a short period can have significant impact on intraoperative risk and postoperative outcomes, especially in patients with severe PAH [35, 36]. Children on multiple therapies may be unsafe to proceed with an intervention without a period of optimization, or a procedure may preferably be done at the bedside, avoiding the triggering effects of motion, temperature change, and stimulation on pulmonary vascular resistance (PVR). Chapter 33 has a comprehensive review of the assessment, therapy, and potential outcomes for children with CHD and PAH.

The neonates and premature infants

Neonates and premature infants continue to present the most critically ill group of patients with CHD requiring preoperative evaluation and urgent interventions. Early recognition and appropriate preparation result in a significant improvement in outcome. The American Heart Association (AHA) thus recommends routine oximetry screening on all neonates prior to discharge to prevent delayed diagnosis of critical CHD. The estimated sensitivity for detection is 70% and the risk of false-positive screening oximetry that results in further evaluation is only 0.035% of infants screened within 24 hours of birth [37].

There is a significant negative linear relationship between perioperative mortality of preterm and near-term infants with CHD and gestational age, decreasing significantly for the same lesion as gestational age approaches 40 weeks [38]. It is also evident that the neurodevelopmental outcome, studied as various domains of language, cognition, and visual or fine motor skills up to 4 years of age, is improved in infants and children with various CHDs when delivery (spontaneous or elective/induced) is at 39–40 weeks' gestation [39]. The preoperative preparation and multidisciplinary discussion should examine the gestational age of the fetus with CHD and the best timing and location of delivery for a neonate with critical CHD [40].

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Although small for gestational age and low birth weight are strong independent predictors of mortality in the first year of life following repair of CHD [41], delay of interventions neither compromises nor improves the outcome. For neonates <2 kg, survival following surgical or interventional repair of CHD was determined by prenatal diagnosis (improved), type of cardiac lesion (worse), with defects including pulmonary venous malformations, and associated extracardiac defects [42].

Medications

Children with CHD are often taking numerous medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) beta-blockers, anti-arrhythmics, and digoxin. These medications should be continued preoperatively until the time of the surgical procedure. Reports in the adult literature suggest that ACE inhibitors and ARBs may cause prolonged hypotension during anesthetic induction and should be discontinued at least 24 hours prior to the surgical procedure [43]. Digoxin is discontinued 24 hours prior to the surgical procedure, as serum levels may be potentially toxic postoperatively [44, 45]. The American College of Chest Physicians recently published guidelines for antithrombotic therapy in children [46]. Children with systemic-to-pulmonary artery shunts, a history of shunt or conduit thrombosis, mechanical or biological prosthetic heart valves, transcatheter interventions or device placement, treatment of Kawasaki disease, and risk factors for the thromboembolic phenomenon, such as bicaval pulmonary anastomosis, are often taking antithrombotic therapy. No specific guidelines exist for discontinuation of antithrombotic medications prior to elective surgery in children. Aspirin irreversibly inhibits cyclooxygenase for the life of the platelet, approximately 10–14 days [47]. Clopidogrel also irreversibly inhibits platelet aggregation. A child taking preoperative aspirin and/or clopidogrel to maintain shunt patency should continue these medications, as the risk of shunt thrombosis is greater than that of perioperative bleeding. Immediately discontinuing aspirin preoperatively does not reduce the risk of perioperative bleeding, given aspirin's long half-life. There should be a discussion with the child's cardiologist, surgeon, and anesthesiologist regarding the optimal timing for stopping these medications. Children who are taking warfarin for their antithrombotic medication should discontinue the warfarin 3–5 days prior to the surgical procedures. The international normalized ratio will usually fall below 2.0 in approximately 2–3 days and will normalize in 4–6 days [48]. Patients should be admitted 2–3 days prior to the surgical procedure to start a bridging regimen of IV heparin. Cessation of the IV heparin 3–6 hours prior to the surgical procedure does not increase the risk of perioperative bleeding [49].

Prostaglandin E_1 (Alprostadil) maintains ductal patency in ductal-dependent lesions, such as pulmonary atresia with or without VSD, tricuspid atresia, HLHS, interrupted aortic arch, or severe coarctation of the aorta. The dose, usually between 0.0125 and 0.1 μg/kg, is adjusted to maintain appropriate oxygenation without signs of over-circulation, decreased systemic diastolic blood pressure, and appropriate acid-base status. Common side effects of prostaglandin E_1 infusion include apnea, fever, flushing, tachycardia or bradycardia, and platelet dysfunction; rarely, cardiac arrest can occur, with the prostaglandin being a contributing factor.

Children who have undergone heart or lung transplantation are often taking multiple immunosuppressive medications that should be continued through the perioperative period to reduce the risk of acute rejection. Finally, children who are taking other medications, such as those for reactive airway disease, gastroesophageal reflux, and seizure disorder, should continue these medications until the surgical procedure (Box 18.1).

Box 18.1: Examples of pre-anesthetic medication instructions

Medications to be continued until the procedure:
- Beta-blockers
- Anti-arrhythmics (unless instructed by electrophysiology to hold)
- Anti-seizure medications
- Pulmonary hypertensive therapy
- Thyroid replacement
- Asthma and COPD medications

Medications to be held the morning of the procedure:
- Diuretics
- Hydralazine
- Nifedipine
- Oral hypoglycemics

Medications to be held 12–24 hours prior to the procedure:
- ACE-inhibitors and angiotensin receptor blockers
- Theophylline

Medications that may be held for several days and require a discussion:
- Anticoagulants (coumadin, antiplatelet agents, heparin related agents)
- Herbal medications

Medications that need planning relative to start time on the day of the procedure:
- Insulin infusions and insulin pumps
- Heparin infusions

Electrocardiographic evaluation, pacemakers, and defibrillators

Children with CHD frequently have rhythm disturbances that require anti-arrhythmic therapy and are manifest on a preoperative ECG. A 12-lead ECG with adequate length of lead II recording for diagnosis of arrhythmias and assessment of changes from baseline is an important component in the evaluation for cardiac surgery. Even if it is "normal" (i.e., normal sinus rhythm without any evidence of chamber enlargement or repolarization abnormalities, etc.), the formal 12-lead ECG serves as a comparison to the postoperative state if ECG changes are suspected and thus should be obtained before any cardiac surgery. If the patient has a history of significant arrhythmia or suspicion for changing rhythm status, a 24-hour Holter monitor is an extremely valuable test to assist in planning for the management of cardiac rhythm during the procedure. Chapter 22 presents an extensive discussion on ECG and arrhythmia analysis and treatment.

Pacemakers and implantable cardioverter defibrillators, collectively referred to as cardiac rhythm management devices

(CRMDs), are commonly used in children with CHD due to either congenital, acquired, or iatrogenic rhythm disturbances. These devices may be placed temporarily (postoperatively) or as permanent due to intrinsic heart disease (common with CCTGA and cardiomyopathies) or they may be acquired following cardiac operations due to scarring, patches, and morphologic chamber changes (as with repaired tetralogy of Fallot). The preoperative period is a critical time to prepare the child with a CRMD for a safe perioperative period. The primary step is to obtain a detailed history of the indication, timing, and type of device placed. Devices have a standard nomenclature established by the North American Society of Pacing and Electrophysiology (NAPSE). An understanding of the position/nomenclature used is essential: I, chamber (s) paced; II, chamber(s) sensed; III, response to sensing; IV, rate modulation; V, multi-site pacing capability. It is important to obtain an ECG to identify pacer spikes and rate, and a chest radiograph to examine the location of the generator and the pacing leads/wires. The CRMD should be interrogated by a programmer, a manufacturing consultant, or an electrophysiologist and its battery life examined [50]. Children are more vulnerable than adults to faster battery generator utilization (due to heart rate) or dislodged/fractured leads (growth changes) or to receiving inappropriate shocks, as shown in a large pediatric CRMD series [51]. The CRMD should be reprogrammed for elective surgery to an asynchronous mode at a rate appropriate for the age and metabolic demands of the patient and the planned procedure, with all anti-tachycardia function turned off. The location of the generator must be clearly marked and noted to plan the necessary approach to avoid or limit electromagnetic interference intraoperatively [52]. For urgent or emergency procedures, a magnet may be placed on a CRMD to revert the device to a fixed rate, asynchronous pacing mode where no cardiac activity is sensed. Caution must be used when applying a magnet, as the preset rate may not be sufficient for the metabolic demands and may be dependent on the battery voltage and life of the generator. A regular 90 Gauss magnet will deactivate the anti-tachycardia function of an implantable cardioverter-defibrillator, but not reset an asynchronous pacing mode. Thus, for all children with a CRMD, whether the device is reprogrammed or a magnet is used, perfusion must be monitored with a waveform monitoring device (pulse oximeter or arterial line wave) throughout the operative procedure until the magnet is removed or the device is interrogated and reprogrammed [53]. Chapter 22 contains a detailed discussion of the management of CRMDs.

KEY POINTS: PREOPERATIVE EVALUATION

- A detailed history of cardiac symptoms, diagnostic and therapeutic procedures, and complications is crucial for peri-anesthetic planning.
- Non-cardiac problems, such as genetic or dysmorphic syndromes leading to difficult airway management, are frequently encountered in the CHD population.
- CHF, PAH, neonatal and premature patients, medication management, and pacemakers and defibrillators all deserve special attention in CHD patients.

Laboratory evaluation

Standard laboratory testing for all children undergoing cardiac interventions must include an assessment of the hematologic status, coagulation testing, serum electrolytes, and kidney function tests (creatinine and blood urea nitrogen [BUN]). Liver function tests (bilirubin, aspartate aminotransferase, and alanine aminotransferase) are assessed when there is suspicion of hepatic dysfunction. Preparation of components for blood transfusion is essential and will require antibody screening and cross-matching. The hemoglobin concentration may reveal anemia and necessitate priming of the cardiopulmonary bypass (CPB) circuit with red blood cells. Children with chronic hypoxemia have significant hematological consequences. Chronic hypoxemia increases erythropoietin activity, increasing hematocrit, hemoglobin, and viscosity, and allow increased oxygen delivery without a sustained increase in cardiac output. However, oxygen delivery can be reduced from red cell rigidity if the hematocrit exceeds 65% [54]. Hyperviscosity is associated with cerebral arterial and sinovenous thromboses, particularly in those children who are dehydrated, have fever, or have iron deficiency. All children with chronic cyanosis should have preoperative hemoglobin and hematocrit. Hematocrit >60% is an indication for preoperative IV fluid therapy. Preoperative phlebotomy is not advocated unless the child is experiencing severe symptoms of hyperviscosity syndrome, such as headaches, dizziness, impaired mental status, visual disturbances, muscle weakness, or paresthesias in the absence of dehydration or iron deficiency [55]. Repeat phlebotomies have been shown to increase the risk of cerebrovascular accidents by causing chronic iron deficiency, resulting in microcytosis and increased blood viscosity. Volume resuscitation and iron replacement therapy should be started prior to elective phlebotomy. Approximately 20% of children with polycythemia have other abnormal hematologic laboratory tests, including prolonged prothrombin and thromboplastin time, thrombocytopenia, platelet dysfunction, hypofibrinogenemia, and accelerated fibrinolysis [29]. Furthermore, all children with CHD undergoing CPB are at risk for intraoperative and postoperative hemostatic derangements. A baseline platelet count, prothrombin time, partial thromboplastin time, and fibrinogen level should be evaluated preoperatively in all children. A screen for antibodies and a crossmatch for RBCs should be performed to ensure that compatible blood is available, particularly for a child who may have had prior exposure to blood products and developed serum antibodies.

Serum electrolytes should be evaluated in children taking diuretics or ACE inhibitors, as both may result in a significant imbalance in the metabolic state. Neonates and infants are at risk for both hypoglycemia and hypocalcemia [56]. This is more prevalent in patients with specific syndromes (as Beckwith–Wiedemann) and those receiving parenteral nutrition. Signs and symptoms of hypoglycemia and hypocalcemia are subtle in neonates and infants, including jitteriness, fussiness, tachypnea, and tachycardia. Children with DiGeorge syndrome, with abnormal parathyroid gland dysfunction, are at risk for perioperative hypocalcemia and should have a preoperative calcium level evaluated. They are

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also at risk for infections due to immune deficiency and will require irradiated blood products whenever needing a transfusion. Children with Down syndrome have an approximately 10% incidence of congenital or acquired thyroid dysfunction and should have preoperative thyroid function tests performed [57]. Preoperative arterial blood gases may reflect the degree of cardiopulmonary reserve. An arterial PaO_2 of 30–40 mmHg and peripheral O_2 saturation <70% indicate poor cardiopulmonary reserve. Metabolic acidosis, assessed from base status, anion gap, and lactate, reflects maldistribution of cardiac output, particularly in those children with ductal-dependent systemic circulation and CHF. Preoperative BUN and creatinine should be assessed in children who are at risk for reduced systemic perfusion and perioperative renal impairment.

KEY POINTS: LABORATORY EVALUATION

- Hemoglobin level is a key preoperative laboratory value, with elevated levels indicating compensatory response to chronic hypoxemia.
- Platelet count, prothrombin and partial thromboplastin times, and fibrinogen level should be obtained before cardiac surgery.
- Electrolytes and BUN/creatinine should be assessed in patients on diuretic therapy.
- Other laboratory tests are guided by signs/symptoms, and previous history of organ dysfunction (e.g., hepatic, hypoglycemia, hypocalcemia).
- A 12-lead ECG is an important diagnostic tool before cardiac surgery.

Preoperative imaging studies

Imaging is essential to identify subjects with CHD to establish the need for treatment and the optimal mode of treatment, define anatomy and hemodynamics for treatment planning, monitor for complications after treatment, and determine the appropriate timing of repeat intervention. In the preoperative period, imaging is required to assess pulmonary vascularity, clarify hemodynamic status, confirm cardiovascular anatomy, determine airway patency, assess the position of vital catheters and tubes, and screen for acute conditions such as hemorrhage, edema, or infection.

Commonly used imaging modalities include chest radiography, echocardiography, cardiac catheterization, MRI, and computed tomography (CT). There are some overarching considerations for imaging utilization in the setting of CHD. Chest radiographs provide essential preoperative information about pulmonary vascularity and physiology of CHD as well as the status of the vital lines and tubes. Transthoracic echocardiography (TTE) is the most important preoperative diagnostic imaging tool in the majority of situations but is less reliable with poorer acoustic windows as patients age and in the postoperative state. Cardiac catheterization is used less frequently for diagnosis but is essential to determine pulmonary to systemic blood flow, and saturations and pressures in cardiac chambers and vessels in complex lesions. Cardiac MR (CMR) is a noninvasive modality that is excellent for a comprehensive assessment of cardiac morphology and function but requires sedation or anesthesia in young children. Cardiac CT is excellent for extracardiac anatomy and is a brief study that requires minimal to no sedation. The choice among cardiac catheterization, echocardiography, CT, or MRI for diagnostic anatomic information frequently benefits from the multidisciplinary discussion. All imaging modalities have a role in preoperative evaluation, preparation, and decision-making, and their relative utility depends on the specific disease and natural history. A good example is the assessment of the child with CHD and pulmonary hypertension, where all investigative procedures contribute important complementary information for the evaluation of the cause, degree, reactivity, and prognosis of pulmonary hypertension [58].

Chest radiography

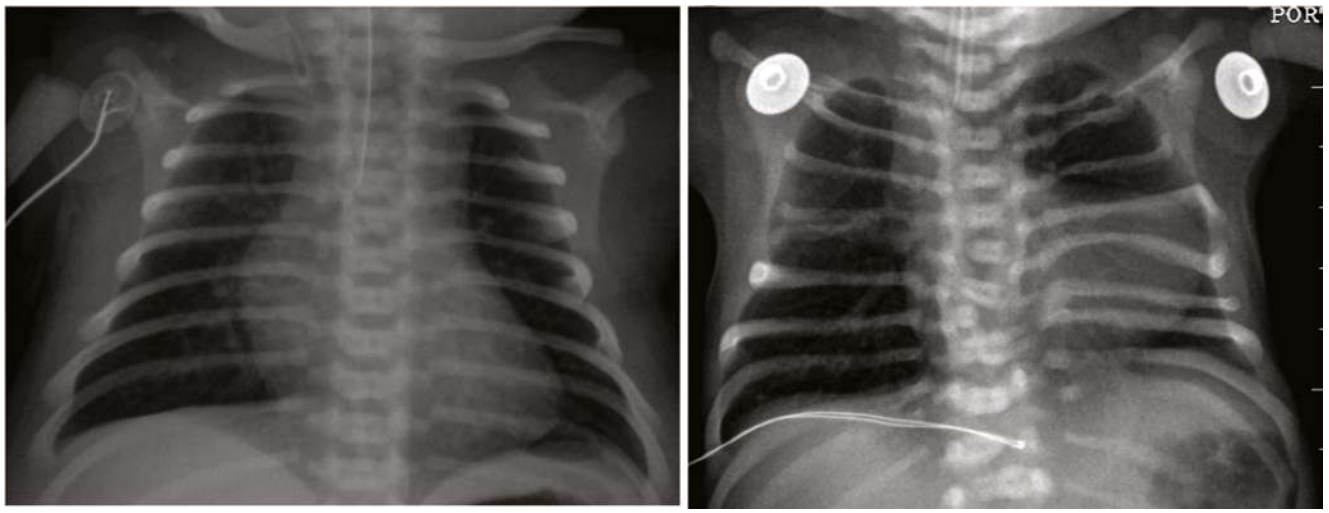
In an era of advanced technology and continuous refinement of imaging modalities for greater safety, efficiency, and accuracy, the role of the humble chest radiograph may be questioned. However, a careful review of a preoperative chest radiograph is essential for the best preparation of a patient with CHD scheduled for cardiac intervention.

The chest radiograph provides pertinent information about the cardiac size and chamber enlargement. A significant increase in the cardiothoracic ratio (>0.5) reflects cardiomegaly, which can be due to increased volume load to a cardiac chamber, valve regurgitation, or poor function with cardiac dilatation. A careful examination of the bronchovascular markings and lung fields can differentiate between children with a significant increase in pulmonary blood flow and those with obstruction to flow due to either anatomic or physiologic etiology [59] (Figure 18.1).

The chest radiograph also provides information on the airway, especially in patients with risk of vascular mediated airway compromise (vascular ring, pulmonary sling, enlarged pulmonary arteries, aneurysmal aortic dilation) [60].

The surgical and anesthesia teams must review the chest radiograph prior to any repeat sternotomy, to prepare for the potential risk of vascular structure injury during dissection. A narrow retrosternal space on lateral radiograph reflects an adherent vascular anatomy with risk of injury to the innominate vein, right ventricle, or a pulmonary artery conduit [61].

Similarly, chest radiographs provide information on the location of vascular lines (especially umbilical catheters in neonates), which can help them with the decision to use them during the procedure for valid pressure monitoring and various medication infusions. Umbilical venous lines located in the hepatic silhouette may not have passed through the ductus venosus and carry the risk of portal vein thrombosis [62]. Using umbilical artery catheters for blood pressure monitoring and blood gas sampling carries significant risks of renal artery thrombosis and lower extremity emboli, if present at or below the renal arteries, and should ideally be identified at the level of the third lumbar vertebra on chest radiography [63, 64].



(A) (B)

Figure 18.1 Chest radiography. (A) Newborn with dextro-transposition of the great arteries, the egg-on-string appearance of the cardiac silhouette and increased pulmonary vascularity. (B) Newborn female with tetralogy of Fallot, ventricular septal defect, pulmonary atresia, ductal-dependent pulmonary blood flow, and decreased pulmonary vascularity. Note the skeletal abnormalities (VACTERL syndrome).

Echocardiography

TTE has long been considered the reference standard in evaluating neonates and children with CHD prior to cardiac interventions. The feasibility of obtaining clear images with multiple acoustic windows, easy access, minimal need for sedation, and low-risk results in TTE are the most common imaging tool in the preoperative period. Most anatomic diagnoses can be obtained confidently with TTE, and the reporting process has become well-standardized to provide the anesthesiologist in the preoperative period with information on structural abnormalities, function, chamber size as well as physiologic parameters.

The anesthesiologist should consider the echocardiographic parameters to evaluate a specific lesion preoperatively, to clearly understand the anatomy and the degree of decompensation, and to plan the best approach for intraoperative care. Following a stage I repair of HLHS, infants are at risk for recoarctation of the aorta (in 20% of patients) at subsequent stages of repair. There are useful TTE parameters for evaluating recoarctation, including peak isthmus velocity >2.5 m/s and coarctation index (ratio of the narrowest region of the descending thoracic aorta to the distal descending aorta diameter) <0.7, which can guide the preoperative risk assessment [65].

A review of TTE to evaluate ventricular function is important, especially in the presence of confounding variables that can bias the estimation of function, such as valvular regurgitation with a large ejection fraction. In patients with significant mitral regurgitation, ventricular dysfunction may be difficult to assess in the preoperative evaluation. Useful echocardiography tools include attention to the regurgitant fraction, the effective ejection fraction, and a higher E/E ratio (ratio of mitral peak velocity to early diastolic velocity of the mitral annulus), which are associated with increased mortality and adverse outcome [66].

An understanding of the morphologic parameters that identify a borderline left or right ventricle is important in the preoperative evaluation of children with CHD. In children with a hypoplastic tricuspid valve, and a borderline right ventricular chamber, parameters including atrioventricular valve index (right-to-left atrioventricular valve area <0.5) and right/left ventricular length ratio (<0.7) are useful in the preoperative preparation (Figure 18.2) [67, 68].

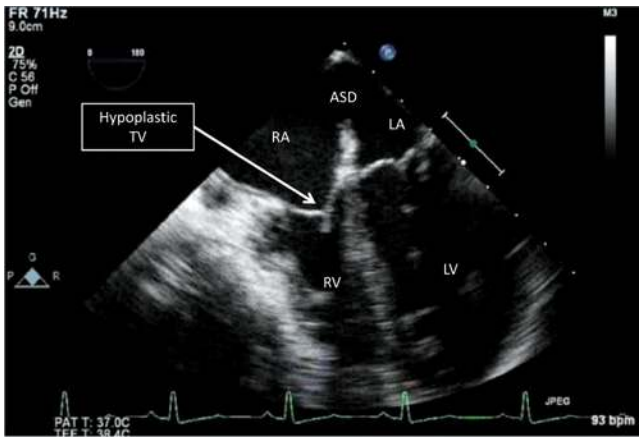


Figure 18.2 Echocardiography: 3-year-old with the hypoplastic right ventricle, small tricuspid annulus, and an atrial septal communication (RV, right ventricle; LV, left ventricle; ASD, atrial septal defect; RA, right atrium; LA, left atrium, TV, tricuspid valve).

However, although a reliable tool in many circumstances, TTE has its limitations. Inter-observer variability in the interpretation of echocardiographic findings affects agreement on anatomic as well as functional data and can significantly impact the planned intervention as well as the extent of anesthetic preparation. Echocardiographic prenatal diagnosis of CHD can have up to 50% variability of anatomic detection of defects [69]. The interpretation of function can also vary significantly among investigators using current guidelines. In a study of 175 children with dilated, hypertrophic and

restrictive cardiomyopathy, agreement among investigators on the grading of diastolic dysfunction was poor (<36%) due to the large range of normal pediatric reference values [70]. The diagnosis of left ventricular endocardial fibroelastosis (EFE) and left ventricular non-compaction (LVNC) can also be challenging. In a series of 104 children with LVNC preoperatively, the agreement between observers on the number and degree of trabeculations was <60%, and on the absolute diagnosis of EFE/LVNC was <67% [71]. Chapter 15 has a complete review of echocardiography applications and limitations in CHD.

Cardiac catheterization

Cardiac catheterization is described in detail in Chapter 34. This discussion will focus on the interaction of cardiac catheterization with other imaging modalities for the diagnosis of CHD, and the role of anesthesiologists in facilitating combined non-invasive and invasive diagnostic evaluations in the same patient encounter.

In the current era, it is rare to use cardiac catheterization for the primary diagnosis of CHD or for evaluation after surgery. The majority of catheterizations in children are performed for planned interventions, or to complete and complement a difficult diagnosis, providing additional diagnostic information to other imaging modalities. Many children with single-ventricle physiology can undergo staged repair without cardiac catheterization [70], with reliance on information from less invasive studies such as echocardiography, CT, and MRI. However, there remains a small subset of children in whom evaluation of the branch pulmonary arteries, reconstructed aortic arch, or coronary arteries is insufficient with TTE, CT, or MRI, and cardiac catheterization is integral in the preoperative evaluation [72].

Similarly, the evaluation of children with idiopathic or CHD-related pulmonary hypertension is critical in the preoperative preparation of these patients. The anesthesiologist should review the catheterization report for the degree of increased PVR, the ratio of right/left ventricular pressure, and the response to pulmonary vascular dilators, most importantly oxygen and nitric oxide inhalation. Patients presenting with catheterization data showing a pulmonary artery pressure >50% of systemic arterial pressure, a PVR of >4 Wood units, and a failure to respond to vasodilator therapy have a significant risk in the perioperative period [73].

The anesthesiologist must review the catheterization report to learn information regarding the complete anatomic diagnosis, associated anomalies, shunt direction and degrees, pressures and gradients, and ventricular function [74]. A demonstration of the value of a catheterization report is presented in Figure 18.3 showing a child with pulmonary atresia and intact ventricular septum who had undergone several staged repairs. The catheterization report can identify important preoperative information, including tricuspid annular size, presence of right ventricular dependent coronary fistulae, and bidirectional Glenn pressure, all of which have prognostic value. The degree and direction of shunting across the atrial septum can be assessed from the stepwise changes of saturation between chambers provided in the catheterization report.

There is an increasing trend towards combining non-invasive imaging like sedated echo, CT, or MR with cardiac catheterization under a single anesthesia encounter. In addition to decreasing the risks related to repeat induction/recovery for separate procedures, this approach also allows complementary information from CT/MR vascular anatomy or MR flow assessment to abbreviate the catheterization protocol accordingly, thereby reducing the need for prolonged sedation or unnecessary radiation exposure. Interventional CMR is also becoming available in more institutions due to recent technological advances with low-field CMR, and MR compatible guidewires and catheters, and will also benefit from a similar hybrid information-gathering approach [75]

A complete review of cardiac catheterization indications, interpretation, and anesthetic management is presented in Chapter 34.

Magnetic resonance imaging

MRI plays an important complementary role to echocardiography in the evaluation of cardiac morphology and function in children with CHD in the preoperative and postoperative periods. Recent technological advancements including free-breathing capabilities, improved image resolution, ultrashort imaging time, and real-time imaging, along with a burgeoning trained user-base, increasing accessibility to MRI scanners, a steady stream of clinical validation studies, and the lack of ionizing radiation have all combined to significantly expand the indications for MRI in pediatric cardiovascular disease over the past several years. Most patients under the age of 8 years who undergo a cardiac MRI study will need either IV sedation or general anesthesia with endotracheal intubation. Endotracheal intubation, often with pharmacologically induced muscle relaxation, is needed if breath-holding is desirable. IV sedation is a preferred alternative to intubation among parents and many anesthesiologists have two important requirements: anesthesiologists experienced in administering IV sedation in patients with CHD; and the ability to modify the MRI sequences for free-breathing acquisition.

Cardiac MRI is a dynamic user-dependent examination, and changes to the protocol will be needed based on real-time evaluation of the initial sequences. The pulse sequences used include [76]:

- *Black-blood sequences* – These sequences provide multi-slice static images, with an excellent spatial resolution with thin slices even in neonates. They provide an overview of vascular anatomy, spatial chamber relationships, airway morphology, and abdominal visceral anatomy, and form an important part of the preoperative evaluation.
- *Bright-blood sequences* – These sequences have an excellent temporal resolution, allowing multi-phase evaluation across the cardiac cycle, and optimal myocardial and blood pool contrast. They are used for ventricular functional assessment and to evaluate valvar morphology and intracardiac morphology, to determine veno-atrial connections, and to track the course of the extracardiac vasculature. Alternatively, free-breathing whole-heart coverage utilizing a three-dimensional steady-state free precession (3D SSFP) sequence with respiratory navigator gating has been

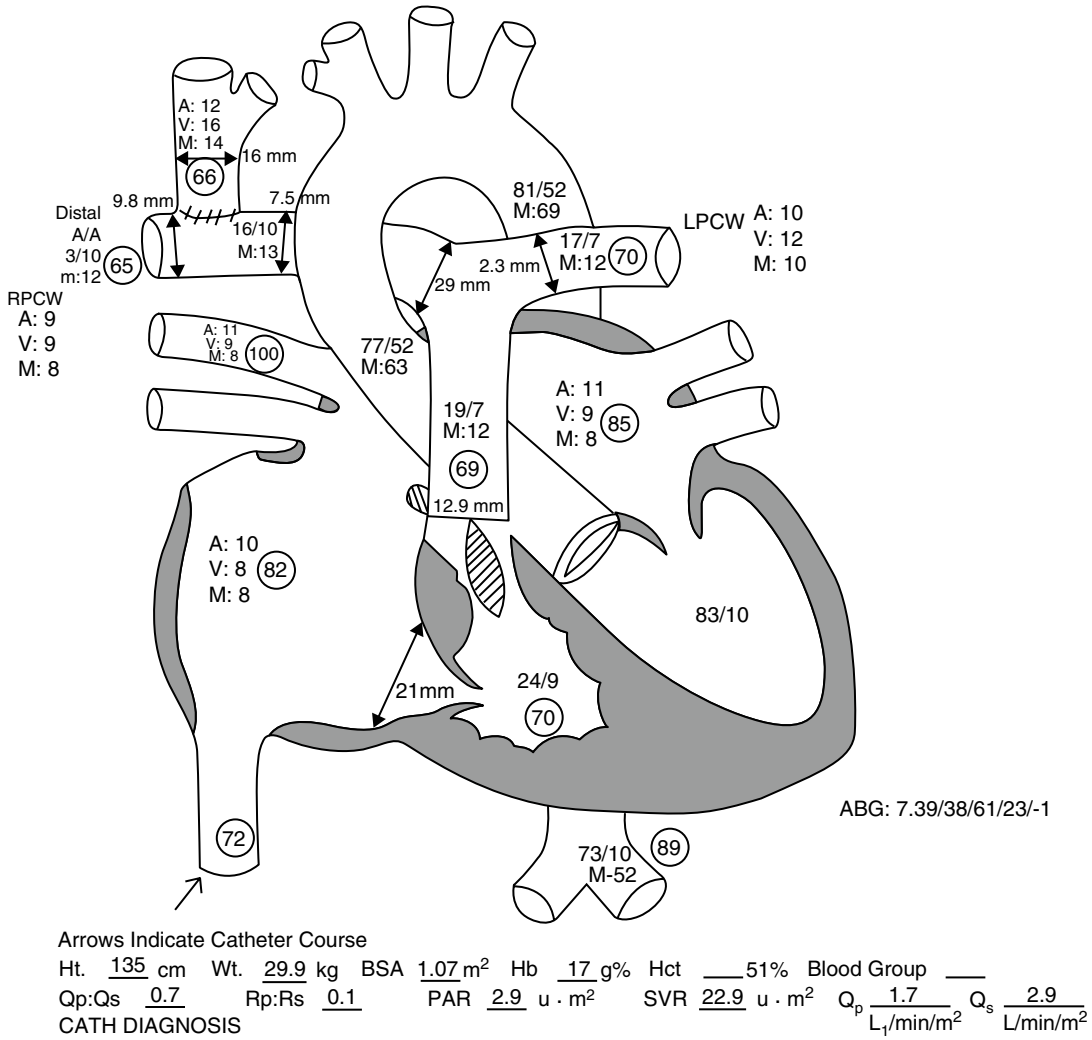


Figure 18.3 Cardiac catheterization diagram of the patient in Figure 18.2 showing anatomy, pressure, and resistance measurements. BSA, body surface area; Hb, hemoglobin; Hct, hematocrit; Qp: Qs, pulmonary to systemic blood flow ratio; Rp: Rs; pulmonary to systemic resistance ratio; PAR, pulmonary artery resistance, Wood units; SVR, systemic vascular resistance; Qp, pulmonary blood flow; Qs, systemic blood flow; ABG, arterial blood gas. A, atrial A-wave pressure; V, atrial V-wave pressure; M–mean pressure. RPCW, right pulmonary capillary wedge pressure (mmHg); LPCW, left pulmonary capillary wedge pressure (mmHg). Circled numbers are measured oxyhemoglobin saturations, uncircled numbers are pressures in mmHg. Numbers followed by mm are diameter measurements.

used to provide comprehensive static, high-resolution morphologic bright-blood evaluation of intracardiac morphology and extracardiac vascular anatomy in one sequence.

- *Flow velocity mapping* – This sequencing is accomplished by a gradient echo-based pulse sequence known as phase contrast. Phase-contrast imaging is based on the principle that moving protons, such as those in flowing blood, when experiencing a specific bi-polar gradient, will accumulate a predictable phase shift that is proportional to their velocity. Phase-contrast imaging can be used to quantify stroke volume, valvar regurgitation, Qp/Qs, differential pulmonary artery flow, venous return, coronary flow, and pressure gradients across stenoses using the modified Bernoulli equation.
- *Magnetic resonance angiography* – The most common sequence used is the contrast-enhanced magnetic resonance angiography (CEMRA) performed in dynamic fashion following bolus injection of gadolinium; this provides a high-resolution three-dimensional (3D) dataset, with its main application being the evaluation of the extracardiac thoracic vasculature, including the pulmonary arteries, pulmonary veins, aorta, systemic veins, and collateral blood supply to the lungs. Techniques of post-processing include multi-plane reformatting, maximum-intensity projection, volume rendering, and virtual angioscopy. Gadolinium contrast agent has recently been discovered to be associated with the development of nephrogenic systemic fibrosis, predominately in adult patients with acute or chronic renal failure. Therefore, thoughtful determination of the benefits and risks in children with CHD is essential.
- Recently, accelerated time-resolved 3D phase-contrast MRI techniques (4D flow) using ECG gating and advanced navigator respiration control have been increasingly used for comprehensive morphological, functional, and flow

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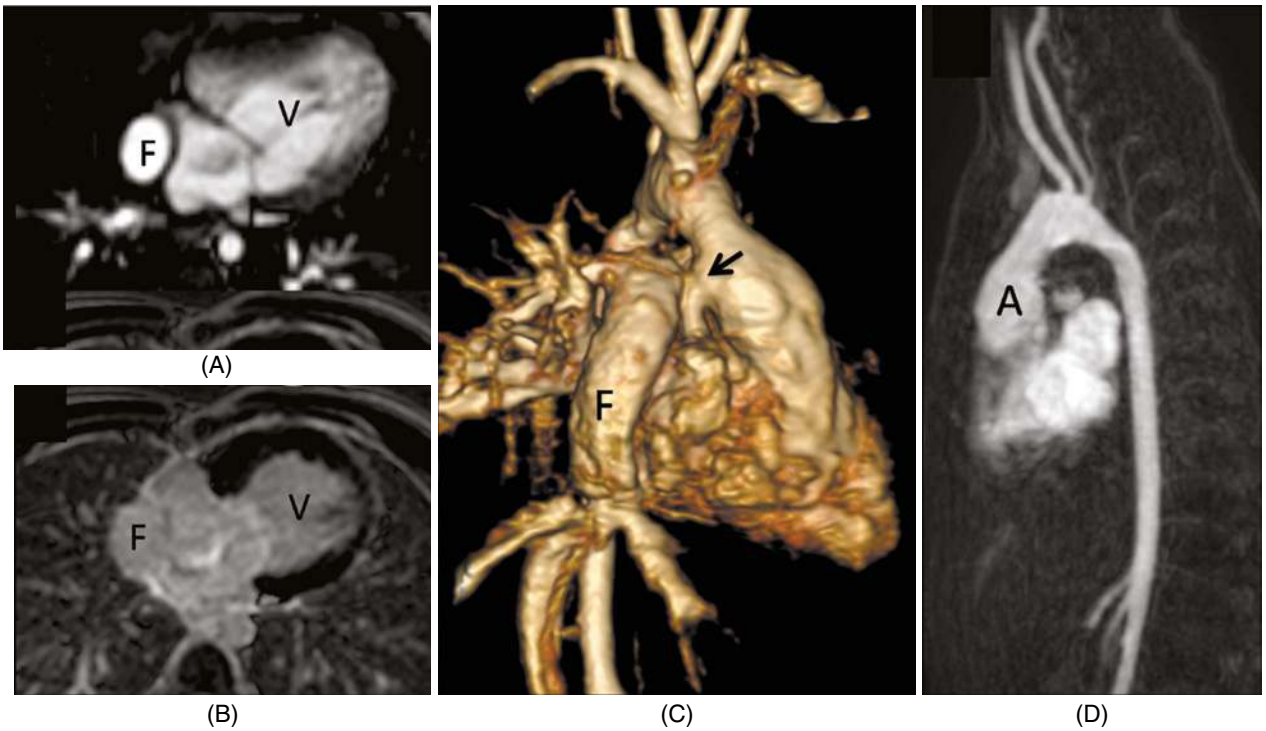


Figure 18.4 A 4-year-old male child with a history of hypoplastic left heart syndrome, status post-stage 3 palliations with an extracardiac Fontan, with a questionable thrombus within the Fontan circuit on echocardiography, for which magnetic resonance imaging was performed. (A) Bright blood image. (B) Delayed enhancement image showing a widely patent Fontan conduit (F) without any intraluminal filling defects to suggest thrombosis. V, ventricle. (C) Anterior projection of a three-dimensional volume rendering demonstrating the entire fat plane from the hepatic veins to the right pulmonary artery, as well as the Damus–Kaye–Stansel anastomosis after a Norwood procedure (black arrow). (D) Sagittal image from a contrast-enhanced magnetic resonance angiogram demonstrating mild neoaortic dilatation and an unobstructed aortic arch after Norwood repair. A, ascending aorta.

evaluation of large vascular geometries. With the addition of blood pool contrast agents to enhance the signal, it is possible to exploit the information in the acquired flow-sensitive 4D data to derive angiographic and functional information, although most sites also perform additional high-resolution angiographic sequences for morphology. Such techniques offer the potential to perform unsupervised free breathing 10–15 minute examinations of children with CHD, requiring minimal or no sedation [77]

The use of MRI has primarily been to define anatomy that is problematic to image using two-dimensional echocardiography, including stenotic branch pulmonary arteries, abnormal pulmonary venous drainage, aortic coarctation, complicated 3D interrelationships, and vascular rings. MRI is the non-invasive gold standard for measurement of ejection fraction, ventricular volumes, regurgitant fraction, differential pulmonary blood flow, and Qp/Qs. The major benefit of MRI compared with other imaging modalities is the complete avoidance of ionizing radiation. Image quality for echocardiography is also limited in older children due to less optimal ultrasound windows because of larger distances with growth; many children have also had previous cardiac surgery, which may affect images due to scar tissue and distortion of anatomic relationships. Particularly in older children or adults who do not require sedation, MRI can be another option for imaging, often adding important benefits beyond echocardiography. Unlike echocardiography, MRI is not done to determine the initial cardiac anatomy but is utilized for the imaging of regions that are more problematic to quantitatively evaluate with echocardiography, including right ventricular ejection fraction and flow into the pulmonary circulation. The perioperative utility of MRI includes an important role in determining the timing of surgery for some lesions. Repeated measurement of right ventricular volume, ejection fraction, and pulmonary regurgitant fraction is now an important tool in decision-making regarding the timing of pulmonary valve replacement after tetralogy of Fallot repair; a right ventricular volume of 170 mL/m^2 or more is an indication for valve replacement used by many institutions [78]. Before superior cavopulmonary anastomosis and Fontan operations (Figure 18.4). MRI is becoming essential for non-invasive imaging of the status of the right and left pulmonary arteries, pulmonary veins, aortic arch, atrioventricular valves, and ventricular function apart from venous and aortopulmonary collaterals [79]. If interventional catheterization procedures are not required before these operations, MRI is increasingly used in lieu of cardiac catheterization to obtain anatomic information as well as some functional data to plan the surgery.

Computed tomography

Congenital heart disease is one of the areas that has benefited tremendously from advances in CT technology. The scientific literature of the 1980s and early 1990s describes the use of helical CT mainly for anomalies involving the great vessels, including diagnosis of pulmonary and systemic venous anomalies, coarctation, and vascular rings. Today, ECG-gated

multi-detector CT is the non-invasive gold standard for coronary artery imaging and has been used for evaluation of cardiovascular morphology, myocardial wall motion and function, valvular morphology and function, myocardial perfusion and viability, vessel wall characterization, postoperative changes and stent patency [80]. It is considered an important complementary modality to echocardiography and MRI for all forms of heart disease.

The latest advances in CT scanner technology including dual-source scanner, wide-detector scanner, higher x-ray tube power, high-efficiency detectors, and improved image processing have further consolidated the role of cardiovascular CT in children, particularly in unsedated patients with higher heart rates. The increased scanning speed could be traded, if desired, for improved longitudinal resolution, increased volume of coverage, or improved image quality. This allows for considerable flexibility in CT protocols, especially in small children who cannot lie still, or cannot suspend respiration.

Sedation is rarely required with current CT scanners, in contrast to MRI, which requires at least sedation, and often general anesthesia in young children. Short scan times have documented utility in critically ill patients, and pediatric patients who are unable to breathe-hold. These techniques have obviated the need for breathe-holding and sedation for most indications even in neonates and infants. However, some indications still require intubation and breath-holding in children who are unable to cooperate, including assessment of coronary CT stenosis, RV dependent coronary circulation, or coronary hooding in William syndrome. The main concerns regarding CT are that ionizing radiation exposure occurs in all cases, and IV contrast is necessary in most. Although the risk posed by radiation from CT is minimal, it is real and must be balanced against the benefits of the examination. When performed for appropriate indications with proper technical parameters, especially in newer generation scanners, the benefits far exceed the very small individual risk. It is important to think in terms of what needs to be seen, rather than what can be seen. The term used for this low-risk approach is "As Low As Reasonably Achievable" (ALARA). Based on the clinical indication, the size of the patient, and the anatomical region of interest, a number of parameters may be adjusted in CT to achieve a high-quality study with the lowest radiation exposure possible. Besides strictly limiting the indications for pediatric CT to those in which diagnostic information cannot be obtained from an alternative non-radiation imaging modality such as echocardiography or MRI, there are several means of decreasing the radiation dose, including confining the study to the anatomical region of interest, using a volumetric technique rather than a helical technique, using a larger pitch, decreasing the tube current (mA) to a minimum, shielding of sensitive areas such as the breast, thyroid, gonads, bone marrow and the eye, avoiding the need for repeat examinations by attention to meticulous technique, including use of proper immobilization and sedation, and restricting the dose-intensive retrospective ECG-gated approach to a few indications which require such a technique, such as coronary artery stenosis imaging. Most questions in pediatric cardiac imaging can be answered with prospectively ECG triggered or un-gated studies, which have significantly lower radiation exposure than retrospectively gated studies.

A number of new applications, covering almost every part of the body, have evolved based on the major advantages offered by the multi-detector scanners: improved volume coverage, temporal resolution, and spatial resolution. Some of these applications include coronary imaging, evaluation of aortopulmonary collaterals in pulmonary atresia (Figure 18.5), ventricular function, high-resolution imaging of the lungs, and dynamic airway imaging (Figure 18.6) [81].

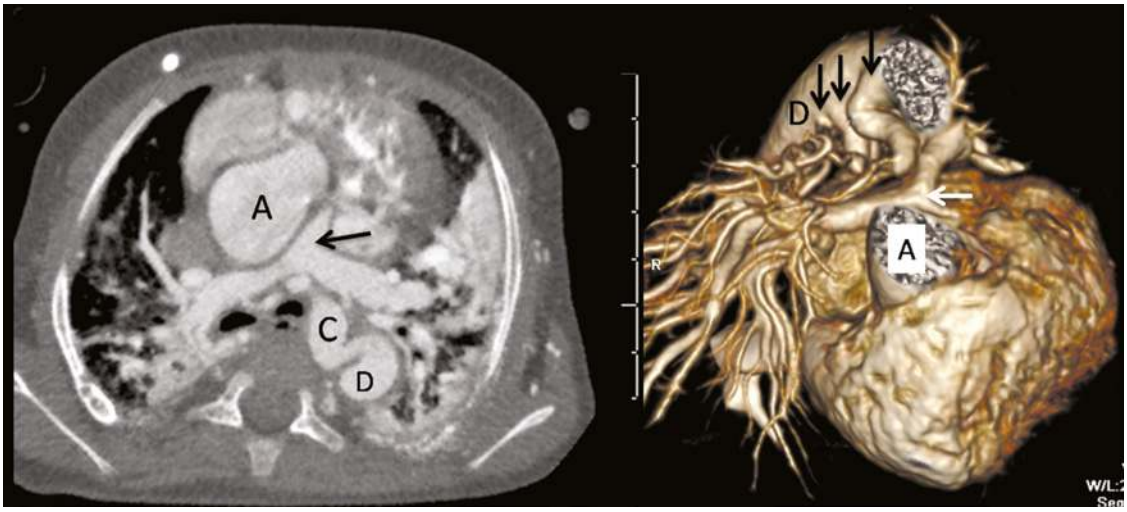


Figure 18.5 One-day-old female with tetralogy of Fallot and pulmonary atresia. A contrast-enhanced computed tomography (CT) scan was ordered to evaluate the status of the pulmonary arteries after echocardiography showed non-confluent branch pulmonary arteries. (A) Transverse image at the level of the branch pulmonary arteries. (B) Right anterior oblique projection of a three-dimensional volume rendering from an unsedated and ungated CT. They clearly demonstrate the confluence of the branch pulmonary arteries (black arrow on A and white arrow on B), and multiple major aortopulmonary collaterals (black arrows on B) arising from the descending aorta (D). Labels: A, ascending aorta; C, largest collateral from the descending aorta.

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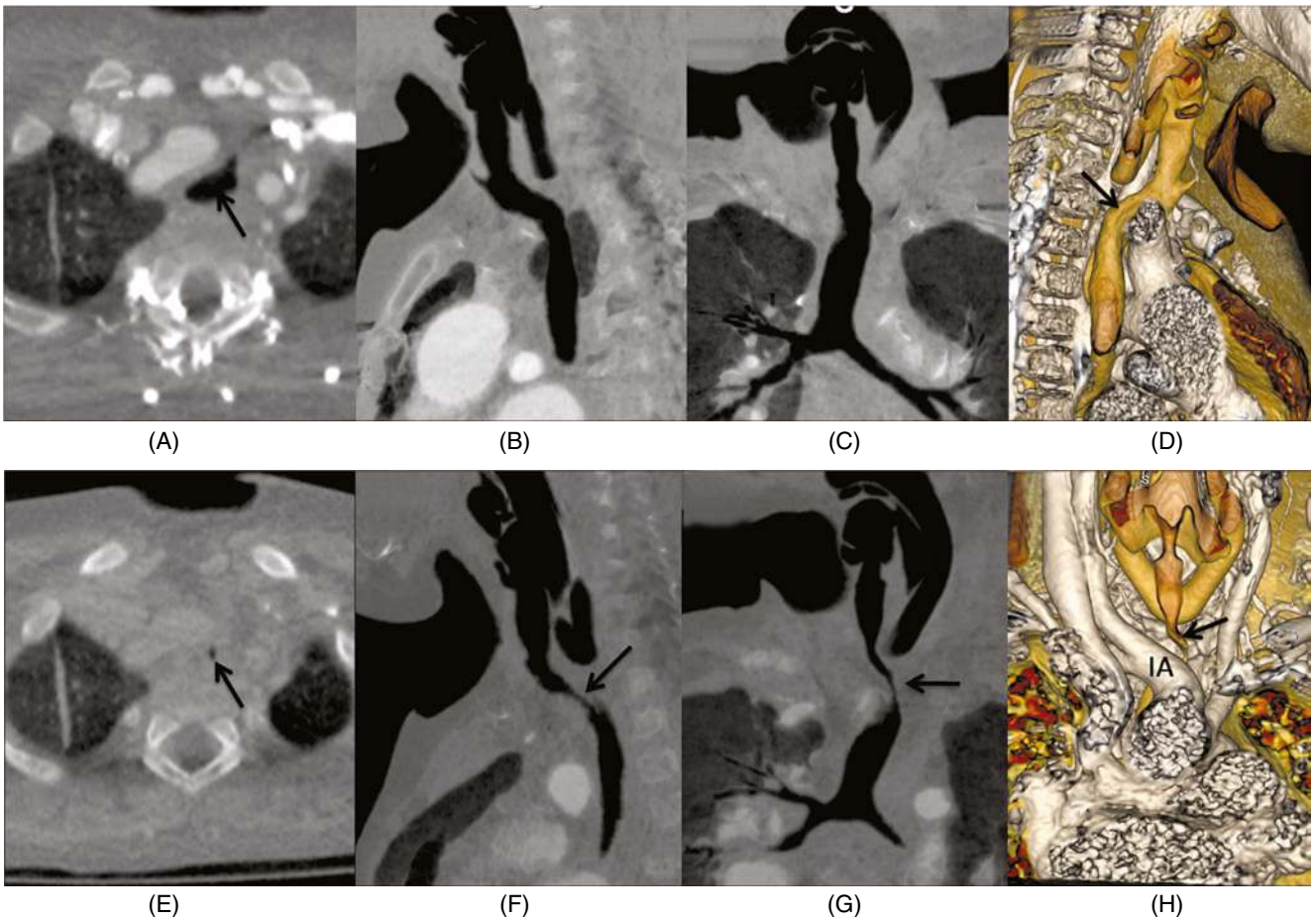


Figure 18.6 A 3.5-year-old female with a history of bilateral lung transplant secondary to filamin A deficiency, presenting with severe stridor related to innominate artery compression of the trachea. Dynamic computed tomography (CT) imaging was performed in inspiration (images A–D), and in expiration (images E–H). (A, E) Axial images at the level of the innominate artery crossing the trachea in inspiration and expiration, respectively, demonstrating a widely patent lumen in inspiration, and near-complete collapse in expiration. (B, F), (C, G) and (D, H) are similar paired inspiratory/expiratory images in the sagittal, coronal, and volume-rendered projections, respectively, showing dynamic narrowing of the trachea (black arrow) at the level of the innominate artery (IA).

Choice of echocardiography, CT, or MRI for non-invasive assessment of CHD

Echocardiography plays a central role in the non-invasive delineation of CHD at all ages. The failure rate with echocardiography increases in the postoperative setting and in older children, when acoustic windows diminish. In the preoperative period, there are numerous examples involving the *extracardiac vasculature*, in which the lack of optimal acoustic windows results in the inadequate characterization of pathology by echocardiography. These include aortic coarctation, anomalous pulmonary veins, scimitar syndrome, systemic venous anomalies, branch pulmonary artery stenosis, and anomalous coronaries. The role of MRI and CT in characterizing the extracardiac vasculature in such patients is well established [82]. On the other hand, echocardiography is quite successful, in the vast majority of cases, in delineating the *intracardiac pathology*, including atrial, ventricular and great arterial situs, the segmental connections, ventricular function, the status of the atrial and ventricular septum and the cardiac valves. But, even in expert hands, some intracardiac defects remain difficult to diagnose by echocardiography. There are an increasing number of papers in the literature addressing the role of MRI as a troubleshooting modality in such situations. A good example is decision-making regarding single- vs. biventricular repair in children with borderline hypoplasia of the left ventricle, in which ventricular volumetry using MRI complements the assessment of intracardiac anatomy by echocardiography. In a series of 154 neonates with left-sided obstructive lesions and a borderline left ventricular volume that underwent an acceptable biventricular repair, only 8% had echocardiographic inclusion criteria to have a good long-term outlook after repair [83]. Echocardiography consistently underestimates left ventricular volume, compared with MRI, and may unfairly preclude some patients from a biventricular repair pathway [84].

Imaging with MRI and CT plays an important role in the postoperative setting when echocardiography windows typically diminish. Examples include tetralogy of Fallot, complex two-ventricle repair, and single-ventricle repair. The goals of postoperative imaging are assessment of ventricular and valvular function, surveillance of grafts, conduits and baffles, early detection of complications, and determination of timing of repeat surgical intervention.

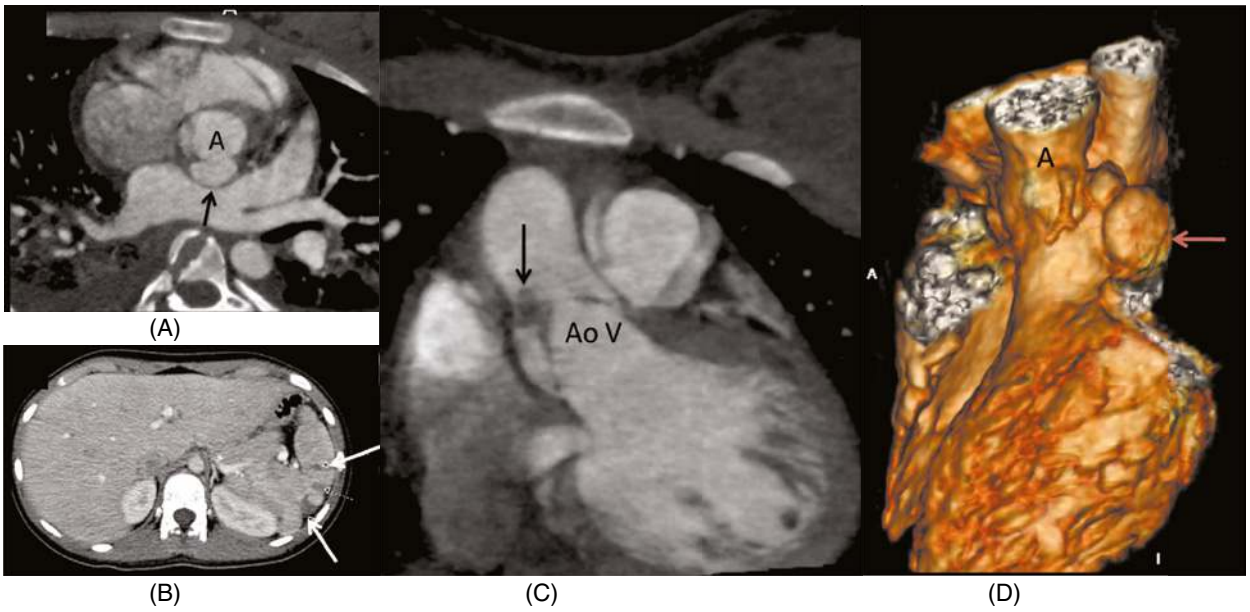


Figure 18.7 Electrocardiogram-gated computed tomography (CT) angiography of the heart in an 18-year-old female with infective endocarditis of the aortic valve and left ventricular outflow tract (LVOT) pseudoaneurysm. (A) Transverse image at the level of the LVOT below the aortic valve demonstrating a 25 × 24 mm wide mouth and extending into the mitral-aortic intervalvular fibrosa. A, ascending aorta. (B) Axial contrast-enhanced image of the upper abdomen demonstrating multiple wedge-shaped hypodensities within the spleen, representing small embolic infarcts. (C) Coronal LVOT view demonstrating thickened aortic valve leaflets (Ao V) and bulky irregular rotations involving the right leaflet. (D) Lateral projection from a three-dimensional volume rendering demonstrating the large subvalvular pseudoaneurysm of the LVOT (pink arrow). CT is helpful for evaluation of the emergent conditions, offering high-resolution imaging of the heart and vasculature without the need for sedation or breath-holding in most cases, and reduces to time spent in the imaging suite. A, ascending aorta.

MRI enjoys a clear superiority over CT for evaluation of intracardiac anatomy, flow, and function. But in situations where the clinical question is restricted to the morphology of the extracardiac vasculature, including the coronaries, pulmonary arteries, aorta, and pulmonary or systemic veins, CT is comparable to MRI (Figure 18.7). Examples of indications appropriate for CT include, but are not limited to, evaluation of total or partial anomalous pulmonary venous return, pulmonary vein stenosis, systemic and pulmonary venous anatomy in heterotaxy, branch pulmonary artery stenosis, confluence and size of branch pulmonary arteries and presence of systemic-pulmonary arterial collaterals in pulmonary atresia, vascular rings, anomalous coronaries, and the presence and severity of coarctation. While MRI provides a more comprehensive evaluation of cardiac form and function in these patients, including calculation of ventricular volumes and function, Qp/Qs, differential pulmonary flow, gradient estimation, and quantification of valvular regurgitation, it is uncertain if the additional information provided by MRI alters clinical decision-making.

There are a few instances where CT is indispensable, as in the presence of pacemakers, aneurysm clips, vascular coils, clips, stents, and thoracic scoliosis rods. CT has the potential to assess the patency of stents or metallic prostheses placed across pulmonary arteries, baffles, coronary arteries, and aortic branches. The spatial resolution of CT is superior to MRI, with the ability to reconstruct up to 0.3 mm in the *z*-axis. Studies have shown that CT is superior to MRI for the evaluation of coronary artery stenosis. One important advantage of CT angiography, when compared with contrast angiography, or even magnetic resonance angiography, is the ability to visualize the vessel wall. CT also provides better delineation of the airway, mediastinal abnormalities, and the pulmonary parenchyma. Other advantages of CT include a reduced need for sedation in young patients, a very short procedure time, and the widespread availability of CT scanners and trained personnel.

In situations where there is a need for serial evaluation, as in the monitoring of aortic root dilatation in tetralogy of Fallot or after a Ross procedure, size of coronary aneurysms in Kawasaki disease, or aortic wall thickness in familial hypercholesterolemia, MRI may be a better choice than CT because of the risk of cumulative radiation dose associated with MRI.

With an increase in awareness of the long-term side effects of sedation, and the advent of new generation CT scanners which freeze respiratory and cardiac motion, decrease radiation exposure by 70 to 80% in children compared with 64 slice scanners, interactive display techniques, and post-processing tools, including 3D printing, and quantitative myocardial and lung perfusion, there has been a significant shift in practice pattern favoring CT over MR for major indications in the setting of CHD.

A comparison between CT and MRI in CHD is given in Table 18.4.

Head ultrasound and other brain imaging modalities

The risk of neurodevelopmental impairment is the most significant concern following repair of CHD, especially in the vulnerable neonatal period. The presence of preoperative neurologic injury increases the risk of extension of the deficit postoperatively and in the long term. However, the most reliable imaging tool to use for neonates to detect brain injury remains controversial. Although head ultrasound (HUS)

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Table 18.4 Computed tomography (CT) and magnetic resonance imaging (MRI) in congenital heart diseases

	CT	MRI
Need for sedation	With new generation scanners, sedation is needed only in a minority of cases, but with 64-slice or older scanners, most children <5 years need sedation	Required in almost all patients <8 years, and most patients <11 years
Duration of sedation	Very short	Long
Intravenous contrast	Excellent safety record, but the risk of an allergic reaction, renal dysfunction, extravasation	No risk of allergic reaction or renal dysfunction Small risk of nephrogenic systemic fibrosis in patients with moderate to severe renal insufficiency
Spatial resolution	Better. True isotropic resolution	Good. Near isotropic resolution
Temporal resolution	Good	Better
Dynamics on angiogram	Multiple dynamics are possible, but not preferred in children due to radiation risk	Multiple dynamics routinely performed, with separation of right-sided, left-sided, and venous structures
Flow	No flow quantification is possible	Flow quantification possible, including stroke volume, Qp: Qs, regurgitant fraction, a gradient across the stenosis
Function	Quantitation of ventricular function possible, but less temporal resolution, along with increased radiation	Quantitation of biventricular function with an excellent temporal resolution
Duration of study	Very short (less than 1 minute)	Long (30–60 minutes)
Contraindications	Acute renal failure, anaphylaxis to iodinated contrast	Pacemakers, AICD
Compatibility with coils, stents and metallic prostheses	Compatible. Metal causes only minimal artifact. Best non-invasive means of evaluating stent patency	Stents and prostheses cause local loss of signal. Hence, stent patency cannot be reliably assessed. Steel coils can cause a large artifact, resulting in a non-diagnostic study. Platinum coils cause less artifact
Health risks	Radiation	Overheating of the body
Ideal indications	Coronary stenosis imaging, anomalous coronaries, emergent studies like aortic dissection or occluded BT shunt, vessel wall evaluation, airway evaluation, need to avoid sedation	Conditions requiring serial studies, screening studies, or conditions requiring evaluation of flow, valvular and ventricular function, and chamber morphology

AICD, automatic implantable cardioverter-defibrillator; BT shunt, Blalock–Taussig shunt; Qp: Qs, pulmonary: systemic blood flow.

continues to be a routine tool in many pediatric cardiac centers, a recent report clearly showed that HUS was not indicated especially in asymptomatic patients. In a series of 167 near- or full-term infants scheduled for cardiac surgery, HUS had evidence of brain injury in 3% of patients compared with 26% on MRI. More importantly, 80% of the HUS findings were false positives [85]. Similar to other reports, abnormal preoperative brain MRI findings are seen in 25–40% of infants with CHD, and correlated with short- and long-term neurodevelopmental impairment. The most common abnormalities seen were white matter injuries, intraventricular hemorrhage, and stroke [86]. Thus, whether there are no symptoms or suspicion of a preoperative injury, routine HUS is not the preferred screening tool, and brain MRI is a more reliable modality. It is important to state that the presence of clinically silent preoperative brain injury on MRI has a low risk of progression and should not delay or preclude clinically indicated and urgent cardiac surgery [87].

KEY POINTS: PREOPERATIVE IMAGING STUDIES

- Chest radiographs are essential preoperative information and play an important role in determining the physiology of CHD.
- Transthoracic echocardiography is the mainstay of preoperative diagnostic imaging but is less reliable with poorer windows as patients age and in the postoperative state.
- Cardiac catheterization is used less frequently for diagnosis but is essential to determine pulmonary to systemic blood flow, PVR, and saturations and pressures in cardiac chambers and vessels in complex lesions.
- Cardiac MRI is a non-invasive modality that is excellent for extracardiac anatomy but requires sedation or anesthesia in young children.
- Cardiac CT is excellent for extracardiac anatomy and is a brief study that requires minimal to no sedation, but it does expose developing patients to ionizing radiation.
- The choice among cardiac catheterization, echocardiography, CT, or MRI for diagnostic anatomic information is complicated and deserves multidisciplinary discussion, including with the anesthesiologist.

Preoperative preparation

Preoperative fasting

The American Society of Anesthesiologists published revised preoperative fasting guidelines in 2017 [88]. These guidelines until recently were the same for children with CHD [89]. Preoperative fasting remains liberalized to allow oral

hydration with clear fluids up to 2 hours prior to the surgical procedure. No increase in gastric volume or acidity has been shown in children with CHD with these liberalized guidelines [90]. Liberal oral hydration is particularly important in children who are cyanotic, polycythemic, those children with outflow tract obstruction, such as hypertrophic cardiomyopathy and aortic stenosis, bicaval pulmonary anastomosis, and shunt-dependent physiology. Children allowed clear liquids on the morning of the surgery were found to be less clinically dehydrated as measured by dry mucous membranes and delayed capillary refill [91]. Preoperative dehydration may be reduced by pre-admitting high-risk children, such as those mentioned earlier, and starting IV hydration until the procedure. If a surgical procedure is delayed, children should be allowed clear oral hydration through the delay. Additionally, liberal oral hydration reduces the risk of hypoglycemia in high-risk children, particularly infants less than 6 months of age who have impaired glycogenolysis and gluconeogenesis and immature glycogen stores. Finally, despite the liberalization of clear oral hydration, *nil per os* (NPO) times should still be verified to reduce the risk of gastric aspiration.

Recently, the need for a minimal period of 2 hours of fasting, and the risk of pulmonary aspiration in children was challenged [92]. Reports have consistently shown the safety of extending clear fluid intake in small children, and even adults to an hour or less prior to the scheduled procedures. Using ultrasound examination of gastric volume, and study of gastric pH, have shown a better physiologic state with less acidosis and accumulation of ketones, more stable hemodynamics at induction and no change in the incidence of aspiration with a liberal approach to fluid intake [93–95]. In addition, the incidence of nausea and vomiting, as well as emergence delirium, is significantly improved. Consequently, multiple societies, including the Society for Pediatric Anesthesia, Association of Pediatric Anesthetists of Great Britain, European Society of Pediatric Anesthetists, and others have endorsed this approach of liberal fluid intake (5 mL/kg) up to 1 hour prior to procedures [96].

Preoperative psychological preparation and premedication

The goal of premedication is to decrease preoperative anxiety, facilitate parental separation, improve cooperation at induction, and reduce sympathetic response at induction. Premedication should be integrated as part of the preoperative assessment. Premedication should not be the rescue solution to the lack of proper preoperative preparation and interaction with the child and family. Preoperative assessment begins with the psychological preparation of the child and the family by developing a rapport with the child and the family. Young children, children with high baseline anxiety, and those with previous negative interactions are at high risk for extreme preoperative anxiety [97]. Pharmacologic premedication is one aspect of multimodal therapies, such as behavioral preparation programs, parental presence at induction, and distraction techniques. Many children have had multiple previous non-cardiac procedures, cardiac surgery, or cardiac catheterizations, and their concerns may be different from the child who has not had been previously anesthetized.

There are multiple benefits to premedication. It eases parental separation and facilitates induction by reducing the amount of inhalational or IV agents necessary for induction. Cyanotic CHD is not a contraindication to premedication. Premedication not only decreases oxygen consumption and increases oxygen saturation in cyanotic children but also achieves sedation and anxiolysis with minimal hemodynamic or respiratory effects. However, respiratory depression with impaired ventilation and oxygenation may occur with multimodal therapy or overdose. An anesthesiologist should be immediately available during and after premedication to monitor ventilation and oxygenation.

Numerous sedative-hypnotics have been used as premedications. Midazolam is the most commonly administered premedication and may be administered by different routes (intranasally 0.3 mg/kg, orally 0.5–1 mg/kg, rectally 0.5–1.0 mg/kg, IV 0.05 mg/kg). The oral route is the most well-tolerated and easily administered. Although increasing doses of 0.75 and 1 mg/kg of oral midazolam are also efficacious, increased ataxia, diplopia, and dysphoric reactions were observed at these higher doses [98]. The nasal route is uncomfortable secondary to the burning sensation and bitter taste. The rectal route has largely been abandoned because the absorption and plasma concentrations are unpredictable. Reliable sedation and anxiolysis were achieved in more than 75% of children at 7.7 ± 2.4, 12.5 ± 4.9, and 16.3 ± 4.2 minutes after intranasal, oral, and rectal administration, respectively [99]. IV midazolam 0.05–0.2 mg/kg is an effective premedication with minimal hemodynamic and respiration effects in those children with an *in situ* IV access.

Intramuscular ketamine 2–5 mg/kg also provides rapid and effective premedication in 5–20 minutes, particularly in those children who are unwilling to accept an oral premedication, secondary to behavioral problems or cognitive issues, or who do not have IV access. Oral ketamine 2–10 mg/kg may also be combined with oral midazolam 0.5 mg/kg to decrease the incidence of adverse events with ketamine and shorten the onset time of anxiolysis. Intranasal sufentanil 2–4 μg/kg is also effective but is used infrequently in children as it may precipitate chest wall rigidity.

Most recently, intranasal dexmedetomidine 0.5–1 μg/kg has been used as a premedication although the onset of action is delayed at 45 minutes [100]. In a meta-analysis of 11 randomized controlled trials, nasal dexmedetomidine was more effective than oral or nasal midazolam as a pre-procedural sedative with a safe profile and no respiratory depression [101]. Dexmedetomidine has been successfully used as a sole agent for sedated transthoracic echocardiography, with a nasal atomizer dose of 1.5–3 mcg/kg in children with cyanotic or acyanotic heart defects, and no desaturation events [102].

Infective endocarditis antibiotic prophylaxis

Infective endocarditis (IE) remains a significant risk for patients with CHD, with a cumulative incidence of 1.1–6/1,000 children, compared with 1.7–6.2/100,000 in the general population. In a large, population-based cohort study of the Quebec CHD Database from 1988 to 2010, the highest risk was with cyanotic lesions, endocardial cushion defects and left-sided obstructive lesions [103]. Invasive dental procedures, cardiac

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surgery within 6 months and age <3 years also increased IE incidence and outcome. The AHA revised the indications for bacterial endocarditis prophylaxis in 2007 [104]. The AHA does not recommend prophylaxis for children undergoing routine gastrointestinal, urologic, and genitourinary procedures with no infected tissue involvement. The indications for bacterial endocarditis prophylaxis have been narrowed significantly compared with previous guidelines and are shown in Box 18.2 and the antibiotic regimens are listed in Box 18.3. Chapter 35 presents additional information about IE prophylaxis.

Box 18.2: Indications for infective endocarditis prophylaxis

- Prosthetic cardiac valve
- History of infective endocarditis
- Unrepaired cyanotic congenital heart defect, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
- Repaired congenital heart defect with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization)
- Cardiac transplantation recipients with cardiac valvular disease

(Source: Adapted from Wilson et al. [104].)

Box 18.3: Treatment regimens for infective endocarditis

Standard general prophylaxis
Amoxicillin
Adult dose: 2 g per os (PO)
Pediatric dose: 50 mg/kg PO; not to exceed 2 g/dose

Unable to take oral medication
Ampicillin
Adult dose: 2 g intravenous/intramuscular (IV/IM)
Pediatric dose: 50 mg/kg IV/IM; not to exceed 2 g/dose

Allergic to penicillin
Clindamycin
Adult dose: 600 mg PO
Pediatric dose: 20 mg/kg PO; not to exceed 600 mg/dose

Allergic to penicillin
Cephalexin or other first- or second-generation oral cephalosporin in equivalent dose (do not use cephalosporins in patients with a history of immediate-type hypersensitivity penicillin allergy, such as urticaria, angioedema, anaphylaxis)
Adult dose: 2 g PO
Pediatric dose: 50 mg/kg PO; not to exceed 2 g/dose

Azithromycin or clarithromycin
Adult dose: 500 mg PO
Pediatric dose: 15 mg/kg PO; not to exceed 500 mg/dose

Allergic to penicillin and unable to take oral medication

Clindamycin
Adult dose: 600 mg IV
Pediatric dose: 20 mg/kg IV; not to exceed 600 mg/dose

(Source: Adapted from Wilson et al. [104].)

Sickle cell disease

The primary clinical manifestations of sickle cell disease are associated crises, including vaso-occlusive, pulmonary dysfunction (acute chest syndrome), and aplastic; infection from splenic dysfunction; and chronic organ damage from chronic sickling, including sickle cell nephropathy, cerebral vascular accidents, and pulmonary hypertension.

There is a concern that CPB may cause sickling and complications such as hemolysis and vaso-occlusive crises from the combined effects of a stressful insult, cooling, and slow red blood cell transit time through the pump. Subsequently, preoperative exchange transfusion is often recommended. There are reports of intraoperative exchange transfusion with the CPB circuit to reduce the sickle cell load [105, 106]. The preoperative transfusion in Sickle Cell Disease Study Group randomized children between an aggressive preoperative exchange transfusion (lowering hemoglobin S to <30%) and a less aggressive simple transfusion (raising hemoglobin to >10 g/dL). Complications related to transfusion were twice as common in the exchange transfusion arm, with no difference in perioperative complications [107]. The exact safe percentage of sickle cell hemoglobin for CPB had never been calculated, but a value of <30%, as with other forms of surgery on these children, has been suggested [108]. Chapter 11 presents additional information about sickle cell disease and CPB.

KEY POINTS: PREOPERATIVE PREPARATION

- Preoperative fasting guidelines are identical for CHD and non-CHD patients; however, CHD patients with systemic-to-pulmonary shunts, cyanosis, and left ventricular outflow tract lesions must not be allowed to become hypovolemic preoperatively.
- Standard premedications, including midazolam, ketamine, and dexmedetomidine, may be used safely in CHD patients, but they must be monitored closely for respiratory depression and desaturation.
- Infective endocarditis prophylaxis is an important consideration in CHD, and the patient's cardiac condition and procedural indication must be assessed to avoid unnecessary antibiotic administration.

Risk stratification

There is an increased risk of perioperative cardiac arrest in children with CHD undergoing both cardiac and noncardiac surgery and diagnostic procedures. The Pediatric Perioperative Cardiac Arrest (POCA) registry reported that 34% of perioperative cardiac arrests over an 11-year period occurred in children with CHD [109]. More than half (54%) of the cardiac arrests in these children were in the general operating rooms, compared with 26% in the cardiac operating rooms and 17% in the cardiac catheterization laboratory. The highest incidence of intraoperative cardiac arrest occurred in children with single-ventricle physiology, and arrests in children with severe aortic stenosis and cardiomyopathy were associated with the highest mortality rates. Three-quarters of

the perioperative cardiac arrests in children with CHD were in children less than 2 years of age, and approximately 75% of the perioperative deaths in children with CHD occurred in children with severe aortic stenosis, cardiomyopathy, and single-ventricle physiology. Additional large databases have also confirmed an increased risk of perioperative cardiac arrest and mortality in children undergoing non-cardiac procedures [110, 111]. Although there are multiple published reports for the management of children with CHD, there is no established methodology to address the magnitude of incremental risk conferred by the degree of severity and compensation of the heart disease [112–118]. The methods available for predicting risks in children with CHD, such as the Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, the Aristotle Basic Complexity (ABC) Score, the original Society of Thoracic Surgeons and the European Association for Cardiothoracic Surgery Mortality score (STS-EACTS score), and the more recently developed Society of Thoracic Surgeons STAT Score are limited to children undergoing only cardiac surgery. These scores risk-stratify children on the complexity of the cardiac surgical procedure rather than the underlying pathophysiology and child's degree of clinical compensation [119–121]. The Risk Adjustment in Congenital Heart Surgery-**1** (RACHS-1) stratifies anatomic diversity into six categories based on age, type of surgery, and in-hospital mortality, using in-hospital mortality as the outcome measure. Category 1 has the lowest in-hospital mortality and category 6 has the highest (Table 18.5). The RACHS-1 method was developed to adjust for baseline case-mix differences for comparing discharge mortality, using a combination of judgment-based and empirical methodologies. The ABC Score assigns a score to each operation, ranging from 1.5 to 15 (with 15 the most complex, based on the primary procedure of the operation). Each procedure is next assigned an index level, which is an integer range of 1 through 4, based on the initial basic score. The ABC Score provides a broad generalization of complexity by dividing surgical procedures from complexity levels. The fundamental principle of the ABC Score is to define the complexity as a constant for the challenge presented by a given surgical procedure. The complexity is the sum of three factors or indices: the potential for operative mortality, the potential for operative morbidity, and the technical difficulty of the operation. The score further discriminates by incorporating two patient modifiers: procedure-dependent factors, including anatomic factors, associate procedures, and age at procedure; and procedure-independent factors, including general factors such as weight. Mortality is calculated on the basis of admission, but only the index operation is analyzed, with the index operation defined as the first operation of the admission that is of operation type "CPB" or "No CPB cardiovascular." The numerator is the number of index operations performed during hospitalizations in which children died before discharge, and the denominator is the number of index operations. The ABC Score classifies more operations, whereas the RACHS-1 discriminates better at the higher end of complexity. The primary objective of the Aristotle Basic Complexity Score is to evaluate and compare surgical management and performance and not predict operative mortality for an individual patient. A recent abstract reported the perioperative complications of children with CHD undergoing non-cardiac procedures using the RACHS-1 score in one tertiary care pediatric cardiac center [122]. The original STS-EACTS estimated procedure-specific mortality that accounted for procedures with a sample size but converted these procedure-specific mortality estimates into a scale from 1.0 to 5.0. The procedures with similar mortality estimates were then grouped into five smaller homogenous categories to minimize within category variation and maximizing between-category variation, allowing for meaningful interpretation of procedures with potentially small sample size. The subsequent STAT CHDS incorporated these STAT mortality categories to identify "positive" and "negative" institutional outliers with identification of centers with similar, higher, and lower center-level mortality rates relative to aggregate rates within each category [123] These comparisons with the revised STAT CHDS can aid in quality assessment and quality improvement initiative (Table 18.6). Unfortunately, these scores are a surgical risk stratification score used to compare inter-institutional perioperative morbidity and mortality

Table 18.5 Risk adjustment for congenital heart surgery score (RACHS-1)

Category	Procedure
1	PDA >30 days
	Coarctation >30 days
	ASD
2	VSD
	TOF
	Vascular ring
	Coarctation <30 days
	AP Window
3	ASO
	TOF/PA
	Ross
	ALCAPA
	DORV repair
	Coarctation/VSD
	BTS
	CAVC
	PAB
4	Truncus arteriosus repair
	Double switch
	Hypoplastic arch repair
	Unifocalization
	Rastelli
	ASO/VSD
	Konno
5	TV repositioning in Ebstein's anomaly <30 days
	Truncus/IAA
6	Norwood Procedure
	DKS

(Source: Adapted Jenkins et al. [119].)
PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; TOF, tetralogy of Fallot; AP, aortopulmonary; ASO, arterial switch operation; TOF/PA, tetralogy of Fallot with pulmonary atresia; ALCAPA, anomalous left coronary artery from the pulmonary artery; DORV, double outlet right ventricle; BTS, Blalock-Taussig shunt; CAVC, complete atrioventricular canal; PAB, pulmonary artery banding; TV, tricuspid valve; IAA, interrupted aortic arch; DKS, Damus-Kaye-Stansel procedure.

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Table 18.6 STAT mortality categories

STAT mortality category	Procedures
1	• Atrial septal defect repair • Vascular ring repair • Ventricular septal defect • Pacemaker generator change
2	• Bi-directional Glenn • Coarctation of aorta repair • Coronary artery origin anomaly repair • Fontan • New pacemaker implantation • Tetralogy of Fallot repair • Valve replacement
3	• Arterial switch operation for transposition of the great arteries • AV septal defect/AV canal repair • Conduit placement • Rastelli procedure
4	• Double outlet right ventricle repair • Interrupted aortic arch repair • Shunt procedures, systemic to pulmonary artery (central or modified Blalock-Taussig) • Total anomalous pulmonary venous connection (TAPVC) repair • Transplant, heart • Truncus arteriosus repair
5	• Damus-Kaye-Stansel procedure • Norwood procedure • Transplant, heart and lung

(Source: Adapted from O'Brien et al. [123].)

following cardiac surgery rather than risk-stratifying children for non-cardiac surgery and diagnostic procedures.

Preoperative risk assessment of adults with acquired heart disease has helped to identify patients at risk for perioperative complications following non-cardiac surgery. Several risk scoring systems have been developed and validated to identify high-risk adult patients undergoing cardiac and non-cardiac surgery, including those by the AHA and the American College of Cardiology (ACC), the EUROSCORE, and the Cleveland Clinic score [123, 124]. The AHA/ACC system risk stratifies clinical predictors of increased preoperative risk into major, intermediate, and minor predictors. These clinical predictors place adults undergoing non-cardiac surgery into high (>5%), intermediate (1–5%), and low (<1%) risk for perioperative complications. Risk adjustment for adult heart disease is potentially easier than pediatric heart disease as there is less variation in anatomy and pathophysiology.

Risk stratification of children with CHD is challenging due to the smaller number of patients and the higher number of procedure types. Six primary requirements are needed to facilitate meaningful multi-institutional analysis of outcomes: common language; mechanism of data collection; the mechanism for evaluating case complexity; the mechanism to ensure and verify completeness and accuracy of the data; collaboration between medical and surgical subspecialties; and mechanism to obtain longitudinal follow-up data. The development of a risk stratification scoring system for children with CHD undergoing non-cardiac procedures may not only help identify children at increased risk for perioperative complications but also aid in resource utilization. For example, it can be used to determine whether the procedure can be performed safely in an outpatient surgery center or whether it needs to be performed in a tertiary center with cardiothoracic surgery and intensive care back-up based on the child's score. Does a poorly compensated child with a high-risk score need to see their cardiologist to optimize medical management prior to their elective procedure? Does that child need additional diagnostic tests or cardiac interventions prior to the procedure? Adult literature on preoperative conditioning has greatly improved outcomes for adults undergoing cardiac and non-cardiac surgery. Simple maneuvers, such as smoking cessation, starting beta-blockers, statins, aspirin, or an exercise program, can mitigate risk. A scoring system may also be valuable for children with CHD. Can we take certain steps to change a child with a high-risk score to a lower score?

Recent studies have attempted to identify high-risk children with CHD for non-cardiac surgery. Faraoni et al. identified predictors for in-hospital mortality in children with CHD following non-cardiac surgery and developed a risk stratification score that can help decision-making and the development of perioperative management guidelines. Eight preoperative markers were strong predictors of in-hospital mortality, including status as an emergency procedure, severe CHD (e.g., children with uncorrected CHD, children with documented pulmonary hypertension, children with ventricular dysfunction requiring medications, or children listed for heart transplant), single ventricle physiology, surgery within 30 days after initial surgery, need for inotropic support, history of pre-operative CPR, acute or chronic kidney injury, and pre-operative mechanical ventilation [124] Scores ≤ 3 were associated with low risk of mortality, scores ranging from 4 to 6 associated with medium risk, and scores ≥ 7 associated with high risk (Table 18.7). Even though this study did identify high-risk children, in-hospital mortality following non-cardiac surgery is a rare event. Although this cohort reported in-hospital mortality of 4.7%, children with minor CHD were excluded from the analysis, making the true in-hospital mortality rate likely much lower [125] Previous studies have reported an in-hospital mortality rate

Table 18.7 Multivariate risk stratification score to predict postoperative mortality

Emergency procedure	Risk score
Severe SHD	+1
Single Ventricle Physiology	+1
Surgery within 30 days	+1
Inotropic Support	+1
Preoperative CPR	+2
Acute or Chronic kidney injury	+3
Mechanical Ventilation	+4

(Source: Adapted from Faraoni et al. [127].)

of 1.06–1.3% in children with CHD following non-cardiac surgery [126]. Furthermore, the data from this cohort was obtained from the administrative database of the ACS NSQIP Pediatric rather than a prospective robust CHD-focused clinical database. Faraoni et al. further attempted to estimate the surgical risk of non-cardiac surgery on the 30-day mortality in children with CHD. The procedure were defined as either low-surgical risk (quartiles 1–3) or high surgical risk (quartile 4) (Table 18.8). Integration of high-surgical risk in the previously above noted factors did not improve prediction of 30-day mortality beyond patient comorbidities and the severity of the cardiac lesion [127]. Lee et al. identified high-risk children for perioperative cardiovascular and respiratory events [128]. Cardiovascular events were defined as inotropic use, cardiac arrest, pulmonary hypertensive crisis, and arrhythmias whereas respiratory events were defined as bronchospasm, laryngospasm, failed intubation/extubation, and oxygen desaturation. The incidence of cardiovascular events was 11.5% and of respiratory events was 4.7%. Age, ASA score ≥ 3, emergency procedure, major and severe CHD, single-ventricle physiology, and mild-severe ventricular function were associated with an increased incidence of perioperative cardiopulmonary complications. These studies have attempted to identify children with CHD at risk for significant perioperative cardiopulmonary complications. A further enhanced risk stratification tool would further identify the degree of pathophysiologic derangement or compensation, helping determine if it is appropriate for the anesthetic to be administered by an anesthesiologist who usually takes care of adults, a pediatric anesthesiologist, or even someone whose practice is limited to pediatric cardiac cases. A score incorporating more detailed patient factors could potentially provide crucial information to the child, the child's family, and the entire perioperative team, including the anesthesiologist, the surgeon, the cardiologist, and the pediatrician. A sample, but

Table 18.8 Classification of surgeries with high-intrinsic surgical risk

Classification	List of surgeries
Gastrointestinal	• Esophageal gastric, enteric, colon (resection/anastomosis) • Pancreatic • Hepatobiliary (resection/anastomosis) • Correction of malrotation (Ladd procedure) • Correction of large omphalocele/gastroschisis • Paraesophageal hiatal hernia repair (including fundoplication) • Imperforate anus repair • Protectomy • Drainage of peritoneal abscess or localized peritonitis
Otorhinolaryngologoy	• Thyroidectomy • Cervical lymphadenectomy
Neurology	• Craniotomy for craniosynostosis • Craniotomy for excision of a brain tumor or AVM (infratentorial or posterior fossa) • Repair of myelomeningocele • Craniotomy trephination
Urology	• Cystectomy (partial or complete) • Nephrectomy (partial or complete) • Pyeloplasty • Ureteroneocystostomy
Thoracic	• Segmentectomy • Pneumonectomy • Thymectomy
Orthopedic	• Arthrodesis (anterior/posterior • Laminectomy • Osteotomy of large bones

(Source: Faraoni et al. [127]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Table 18.9 Sample risk stratification score for children with congenital heart disease

	0	1	2
CHD	Simple	Moderate (ASD/PS)	Complex (TOF/d-TGA)
Repaired CHD	Repaired with no residual	Repaired with residual	Palliated or unrepaired
Obstruction (right- or left-sided)	None	Mild (gradient <40 mmHg)	Moderate/severe (gradient >40 mmHg)
Ventricle	2	1	1 (or 2)
	LV systemic	LV systemic	RV systemic
Systemic ventricular dysfunction	Mild	Moderate	Severe
PVR	Mild	Moderate	Severe
	2 WU	2–4 WU	>4 WU
	PAP <1/2 systemic	PAP ≥ 1/2 and less < systemic	PAP ≥ systemic
SpO_2	>90%	75–90%	<75%
HCT%	30–45%	25–30% and 45–65%	<25% or >65%
Arrhythmias	Rare	Atrial	Ventricular
	Not requiring therapy		Pacemaker/ICD
Drugs (anticoagulants, anti-arrhythmics, diuretics, inotropes, others)	1–2 categories	2–4 categories	>4 categories
Surgical Severity	Minor (non-invasive or diagnostic)	Intermediate (peripheral)	Major (intracavitary)
Surgical urgency	Elective	Urgent (<24 hours)	Emergent

ASD, atrial septal defect; PS, pulmonary stenosis; TOF, tetralogy of Fallot; LV, left ventricle; RV, right ventricle; SBF, systemic blood flow; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; AS, aortic stenosis; VSD, ventricular septal defect; d-TGA, dextro-transposition of the great arteries; PVR, pulmonary vascular resistance; SpO_2, pulse oximeter saturation; HCT, hematocrit; WU, Wood units; PAP, pulmonary artery pressure; ICD, implantable cardioverter-defibrillator.

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not validated scoring system, may have the advantage of simple application and the ability to quickly identify children with decompensated or high-risk CHD, incorporating various aspects of the child's pathophysiologic condition (Table 18.9).

KEY POINTS: RISK STRATIFICATION

- CHD patients are significantly more likely to suffer cardiac arrest during anesthesia than patients without heart disease; over 50% of arrests occur outside the cardiac operating room or catheterization laboratory.
- There are several risk stratification methods for hospital mortality after cardiac surgery
- Children at high risk for significant perioperative cardiopulmonary morbidity and mortality following noncardiac surgery include those undergoing emergency procedures, severe CHD, single-ventricle physiology, previous surgery within 30 days, preoperative inotropic support, preoperative CPR, preoperative acute or chronic kidney injury, or preoperative mechanical ventilation.
- An enhanced risk assessment strategy for CHD would additionally take into account the degree of pathophysiologic derangement or compensation.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

6 Bacha EA, Hijazi ZM, Cao QL, et al. Hybrid pediatric cardiac surgery. Pediatr Cardiol 2005;26:315–22. Excellent review of the advances in the care for infants with CHD, the various options and the process of collaborative and multidisciplinary care.

10 Franck LS, Spencer C. Informing parents about anesthesia for children's surgery: a critical literature review. Patient Educ Couns 2005;59:117–25. A discussion of the scope of information delivered to parents and the impact on anxiety, preparation of family and child.

28 Kantor PF, Lougheed J, Dancea A, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society Guidelines. Can J Cardiol 2013;5:1535–52. An important review on the best approach to preoperatively assess cardiac function and the degree of decompensation in children with heart disease.

32 Carmosino MJ, Friesen R, Doran A, et al. Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. Anesth Analg 2007;104:521–7. A detailed discussion on the high-risk group of children with pulmonary hypertension and the approach to preoperative preparation and optimization.

50 Navaratnam M, Dubin A. Pediatric pacemakers and ICD's: how to optimize perioperative care. Pediatr Anesth 2011;21:512–1. Detailed review of perioperative care of children with pacemakers and defibrillators. An excellent reference list for other studies and reports.

75 Brown DW, Gauvreau K, Powell AJ, et al. Cardiac magnetic resonance versus routine cardiac catheterization before bidirectional Glenn anastomosis in infants with functional single ventricle: a prospective randomized trial. Circulation 2007;116(23):2718–25. An interesting report demonstrating the changes in imaging studies for children with staged single-ventricle repair.

81 Valente AM, Cook S, Festa P, et al. Multimodality imaging guidelines for patients with repaired tetralogy of Fallot: a report from the American society of Echocardiography: developed in collaboration with the society for cardiovascular magnetic resonance and the society for pediatric radiology. J Am Soc Echocardiogr 2014;27(2): 111–41. An up-to-date review of all imaging modalities, selection criteria and interpretation of the different tools for children with CHD.

103 Rushani D, Kaufman JS, Ionescu-Ittu R, et al. Infective endocarditis in children with congenital heart disease: cumulative incidence and predictors. Circulation 2013;128:1412–9. An update on the risk of infective endocarditis and the indications and medications for prophylaxis in children with CHD.

121 O'Brien S, Clarke D, Jacobs J, et al. An empirically based tool for analyzing mortality associate with congenital heart surgery. J Thorac Cardiovasc Surg 2009;138:1139–53. Demonstration of the surgical approach for risk stratification in congenital heart disease as a template for an anesthesia-related risk stratification scoring system.

123 O'Brien SM, Clarke DR, Jacobs JP, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. J Thorac Cardiovasc Surg 2009;138(5):1139–53. Another enhanced risk-based tool for analyzing mortality in congenital cardiac surgery.

124 Faraoni D, Vo D, Nasr VG, et al. Development and validation of a risk stratification score for children with congenital heart disease undergoing noncardiac surgery. Anesth Analg 2016;123(4):824–30. A new risk stratification scoring system.

128 Lee S, Reddington E, Koutsogiannaki S, et al. Incidence and Risk Factors for Perioperative Cardiovascular and Respiratory Adverse Events in Pediatric Patients With Congenital Heart Disease Undergoing Noncardiac Procedures. Anesth Analg 2018;127(3):724–9. An updated study of risk factors for perioperative cardiovascular and respiratory event in children with CHD undergoing noncardiac surgery.

CHAPTER 19

Approach to the Fetus, Premature, and Full-Term Neonate

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Introduction

The advances in pediatric cardiology and cardiac surgery over the past 35 years have resulted in a substantial decrease in morbidity and mortality associated with congenital heart disease (CHD). Most congenital heart lesions are now amenable to either anatomical or physiological repair early in infancy. Opinion regarding the optimal timing of corrective surgery for infants with symptomatic CHD regardless of their age or weight has undergone radical change over the past several decades. Rather than the previous strategy of initial palliation followed by correction in early childhood, the current approach favors complete repair within days to weeks of birth, if feasible. Advances in diagnostic and interventional cardiology, the evolution of surgical techniques, management of cardiopulmonary bypass (CPB), as well as refinements in postoperative care have all contributed to the successful strategy of early corrective two-ventricle repair. Most recently, this approach has been extended to include premature and low birthweight (LBW) neonates also. However, the low mortality achieved with two-ventricle repairs has not been the experience in LBW neonates undergoing palliation for single-ventricle defects, such as hypoplastic left heart syndrome (HLHS).

Cardiac surgery in the premature and very LBW neonate presents additional challenges for the anesthesiologist. As for any pediatric cardiac procedure, a thorough understanding of the pathophysiology of the heart defect and planned surgical procedure and anticipation of specific postoperative problems are essential. There are further considerations, however, when providing anesthesia to the premature and LBW neonates: immaturity of the airway, lungs, cardiovascular system, liver, kidney, and central nervous system makes these infants more susceptible not only to surgical but also to anesthetic complications. Finally, as the limits for managing CHD continue to be extended, fetal cardiac interventions (FCIs) emerge as the next challenging frontier.

This chapter will describe general principles relevant to anesthesia for the newborn, including the premature and LBW neonate with CHD. The impact of prematurity, the outcome of cardiac surgery in the premature and LBW neonate, and new directions with transcatheter ductus arteriosus stenting and FCIs will be discussed.

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Approach to treatment in the neonate

Early palliation

In the early days of cardiac surgery for neonates, particularly those born prematurely, initial palliation or medical management of congenital cardiac defects was preferred. With technical limitations for various surgical techniques and relatively high risks associated with CPB in small babies, a successful repair often required a certain size or weight. Although the actual "target" weight that a neonate should achieve before the repair was never well documented, newborns with a weight of less than 2.5 kg were considered at higher risk.

The goal of palliative procedures is to control pulmonary blood flow sufficiently to allow for growth, whilst avoiding excessive blood flow to the pulmonary circulation that impairs systemic perfusion and volume overloads in the systemic ventricle. Nevertheless, palliation with a pulmonary artery (PA) band or a modified systemic-to-pulmonary artery shunt, such as a modified Blalock–Taussig (BT) shunt, can be technically demanding procedures in neonates and tend to be even more problematic in those with LBW (see Table 19.1).

Systemic-to-pulmonary artery shunt

While the originally described BT shunt directly connected the subclavian to the pulmonary artery, in contemporary practice a modified version of the procedure is used with an interposition polytetrafluoroethylene (PTFE) (Gore-Tex) graft between the subclavian or innominate artery and pulmonary artery. The size and length of the tube graft as well as the site selected for the proximal anastomosis are critical. A relatively large shunt may lead to excessive pulmonary blood flow, congestive heart failure (CHF), and possible pulmonary vascular obstructive disease (PVOD). Conversely, a small shunt can result in inadequate pulmonary blood flow, lower arterial oxygen saturation (SaO_2), possible shunt thrombosis, and poor growth of the pulmonary arteries making further repair more challenging. Assuming a normal cardiac output and hematocrit, absence of pulmonary venous desaturation and unrestricted mixing of systemic and pulmonary venous return in the atrium, an ideal SaO_2 between 80 and 85% indicates a relatively balanced circulation with a pulmonary to systemic blood flow ratio (Qp: Qs) close to 1:1.

Table 19.1 Complications of palliative surgery

	Early complications	Late complications
Systemic-to-pulmonary artery shunt	Excessive pulmonary blood flow	Distortion of pulmonary arteries
	Heart failure	
	Inadequate pulmonary blood flow	Asymmetrical growth of the pulmonary arteries
	Cyanosis	Pulmonary vascular obstructive disease
	Shunt obstruction: Thrombus Mechanical	
Pulmonary artery banding	Band too loose: excessive pulmonary blood flow	Complications at band site: Distortion and residual stenosis after repair Aneurysm
	Band too tight: inadequate pulmonary blood flow	Complications proximal to band site: Right ventricular hypertrophy Subaortic stenosis Pulmonary valve stenosis
		Complications distal to the band: pulmonary artery stenosis

KEY POINTS: EARLY PALLIATION

- This was the classical approach in the early days of pediatric cardiac surgery due to technical limitations.
- Typical procedures are pulmonary artery banding or systemic-to-pulmonary artery shunt.
- The goal is adequate control of pulmonary blood flow to allow for growth without pulmonary overcirculation, cyanosis, inadequate systemic perfusion, or volume load on the ventricle.
- It is often technically challenging and is associated with many potential early and late complications.
- Recent advances with catheter-based intervention have allowed stenting of the ductus arteriosus to become an alternative to the modified BT shunt in selected patients.

A further problem of a small shunt is the likelihood of outgrowing the shunt size causing progressive cyanosis and requiring earlier surgical intervention. On the other hand, if a larger shunt size (i.e., ≥4.0 mm) is used in a newborn, the excessive pulmonary blood flow may compromise systemic perfusion, cause ventricular volume overload, heart failure, and prolonged postoperative recovery. In our experience, a shunt of 3.5 mm is the optimal size to use in a neonate weighing between 3 and 4 kg. If a 3.0 mm long shunt is used, the risk for acute thrombosis in the early postoperative period is increased, even in LBW neonates. The introduction of anticoagulation with heparin is important once hemostasis has been secured after surgery. Early platelet inhibition with an intravenous glycoprotein IIb/IIIa inhibitor may help reduce the risk of early thrombosis [1]. The mortality rate after neonatal modified BT shunt remains high, particularly for infants weighing less than 3 kg. A large multicenter study from the Society of Thoracic Surgeons Congenital Heart Surgery Database reported an in-hospital mortality rate of 7.2% with a 13% rate of serious morbidity in neonates undergoing modified BT shunt placement without concomitant procedures [2]. Patients weighing <2.5 kg had a four-fold increase in odds of death.

KEY POINTS: SYSTEMIC-TO-PULMONARY ARTERY SHUNT (E.G., MODIFIED BT SHUNT)

- Shunt geometry is critical.
- If the shunt is too large, there is a risk of pulmonary overcirculation, CHF, and the development of PVOD.
- If the shunt is too small, the risk is of inadequate pulmonary blood flow and cyanosis, shunt thrombosis, and early surgery.
- Late complications are distortion and/or asymmetrical growth of pulmonary arteries, and PVOD.

Transcatheter ductus arteriosus stent

Recent advances in transcatheter techniques and device technology have allowed stenting of the ductus arteriosus to be a successful alternative to surgically placed modified BT shunt in patients with ductus-dependent cyanotic CHD. Although patients undergoing ductal stenting have a higher reintervention rate, retrospective multicenter cohort studies support an early survival advantage and shorter ICU stay for infants with ductal stenting [3, 4]. Ductal stent additionally avoids potential operative complications of modified BT shunt placement including vocal cord paralysis, chylothorax, and surgical site infection.

Attention to the ductal morphology is critically important in planning ductal stent placement. CT imaging, in addition to echocardiography, is helpful to delineate ductal anatomy and plan the access site to achieve the straightest trajectory to the ductus. A ductus off the underside of the aortic arch may be successfully approached with left carotid or axillary artery access. While in the past access to these vessels would usually occur via surgical cutdown, there are increasing reports of the safety of percutaneous access [5, 6]. Technical success can be achieved even with a highly tortuous ductus [7]. Prostaglandin E_1 is typically discontinued 6–12 hours prior to the procedure to ensure the ductus is restrictive prior to stenting. Ductal stenting is not without some risk. Complications include ductal spasm, dissection, thrombosis, and stent embolization. Appropriate surgical and extracorporeal membrane oxygenation (ECMO) backup is essential. Drug-eluting stents may decrease reintervention rates and in-stent stenosis [8]. Although immunosuppressive levels of sirolimus may occur for a prolonged period following neonatal stent implantation, negative outcomes related to immunosuppression have not been reported yet [9]. Dual antiplatelet therapy is commonly used to reduce the risk of stent thrombosis.

Banding of the pulmonary artery

Banding of the main PA to reduce pulmonary blood flow can also be a challenging palliative procedure. If the band is too tight, severe cyanosis may occur, and if the band is too loose, the increase in pulmonary blood flow will contribute to CHF and possible PVOD. Distortion of the pulmonary artery secondary to migration of the band may contribute to both proximal and distal artery stenoses and complicate later repair, but can also lead to right ventricular hypertrophy, subaortic stenosis and pulmonary valve stenosis, depending on the relationship of the great arteries to the ventricular outflow tract. Determining the correct size of a band at the time of surgery is difficult. There are no accurate formulas for band size, and the hemodynamic changes at the time of band placement must be closely observed. Ideally, the banded PA will result in an increase in systemic systolic blood pressure of approximately 20%, and, depending on the underlying pathology, a fall in SaO_2 to around 85% breathing room air. The pressure gradient across the band can also be directly measured. Usually, a pressure difference of approximately 50% proximal to the distal across the band is sufficient. Monitoring hemodynamic changes at the time of PA band placement is essential, and anesthetic techniques that could decrease ventricular function or cardiac output are best avoided. Therefore, an opioid technique is most often necessary, and extubation should be delayed until the hemodynamic effect of the band is determined as the patient emerges from anesthesia and starts to wean from mechanical ventilation.

KEY POINTS: BANDING OF THE MAIN PULMONARY ARTERY

- Difficult intraoperative adjustment with constant monitoring of hemodynamic changes requires a stable anesthetic technique with minimal negative effects on ventricular function.
- The goals are an increase in systemic blood pressure by 20%, a decrease in SaO_2 to 85% on room air, and a pressure gradient of 50%.
- Late complications are migration of the band, distortion, stenosis or aneurysms of pulmonary arteries, right ventricular hypertrophy, subaortic stenosis, and pulmonary valve stenosis.

The case for early complete repair

As noted previously, whenever possible, early two-ventricle repair of congenital cardiac defects is the preferred approach in the modern era. Avoiding the long-term consequences of excessive volume and pressure overload on the ventricles and pulmonary vasculature as well as the potentially detrimental effect of chronic hypoxia, early repair allows for more normal growth and development. The considerable advances in cardiac surgery and CPB techniques have contributed to a dramatic reduction in mortality following cardiac surgery in newborns [10–12], but these patients nevertheless remain at risk for significant end-organ impairment, particularly neurological injury [13].

Medical management alone, with the goal of controlling pulmonary blood flow and volume overload on an immature myocardium, is often extremely difficult and unsuccessful. Long-term effects associated with pulmonary overcirculation, chronic volume and/or pressure load on the ventricles, and cyanosis may substantially alter growth and development and lead to myocardial and pulmonary injury which will influence the outcome of subsequent repairs. In most newborns with a large left-to-right shunt, the imbalance

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Box 19.1: Symptoms and signs of congestive heart failure in neonates and infants

Low cardiac output
- Tachycardia
- Poor extremity perfusion
- Cardiomegaly
- Hepatomegaly
- Gallop rhythm

Increased respiratory work
- Tachypnea
- Grunting
- Flaring of alae nasi
- Chest wall retraction

Increased metabolic work
- Failure to thrive
- Poor weight gain

between pulmonary and systemic blood flow will increase as pulmonary vascular resistance (PVR) falls in the first few weeks of life and the physiologic nadir in hematocrit is reached. The clinical manifestations of an infant with CHF are shown in Box 19.1. Tachypnea and the additional work of breathing, secondary to an increase in pulmonary blood flow and total lung water, raise the metabolic demand and the percentage of the total cardiac output directed toward respiratory muscle work (most notably, the diaphragm). This essentially diverts cardiac output from other metabolically active functions, particularly from the splanchnic circulation and absorption of enteral nutrition. The abnormal circulatory physiology is unable to meet metabolic needs and patients fail to achieve normal growth.

KEY POINTS: EARLY COMPLETE REPAIR

- The current strategy of choice is early two-ventricle repair within days to weeks after birth.
- This is possible with recent advances in diagnostic imaging, surgical and CPB techniques, anesthesia, and postoperative intensive care.
- It avoids the long-term detrimental effects of volume and pressure load on immature ventricles as well as chronic hypoxia and polycythemia on growth and development.

Special considerations for the neonate

Although the risk for early mortality in neonates undergoing cardiac surgery may be increased, randomized and prospective studies comparing early surgery versus medical management in hopes of weight gain in neonates with critical lesions have not been performed. Such has been the nature of many of the advances in CHD management. For example, infants with an increased pulmonary blood flow who undergo delayed surgical intervention often fail to thrive and are at risk of recurrent respiratory infections. Their work of breathing and energy expenditure is significantly increased, and cardiomegaly with hyperinflated lung fields is evident on chest radiograph. Cardiac surgery and CPB may be delayed because of concerns for intercurrent infection and the risk of exacerbation or reactivation of inflammatory lung processes, which in turn may cause intrapulmonary shunting and severe hypoxemia, pulmonary hypertension, and prolonged mechanical ventilation. The early repair or palliation of defects to limit pulmonary overcirculation and volume load on the systemic ventricle will often avoid these complications.

The optimal timing of delivery of neonates with CHD is now felt to be at 39–40 weeks' gestation. The former practice of elective delivery at earlier gestational ages (e.g., 36–37 weeks) is associated with higher mortality and should be avoided unless there are clear maternal or fetal indications [14, 15].

The management of neonates in the immediate postoperative period after a two-ventricle repair can be a challenge, but with substantially improved outcomes, mortality alone is no longer a reliable index against which to measure or compare new or alternative treatments in this group of patients. The focus should rather shift to long-term quality of life, ongoing need for reintervention, and hospital admissions. Survival after palliative procedures in patients with complex single-ventricle defects remains lower, although there has been a steady improvement in mortality and longer-term outcomes [16].

Limited physiologic reserve

Care of the critically ill neonate requires an appreciation of the special structural and functional features of immature organs. The neonate appears to respond more quickly and extremely to physiologically stressful circumstances; this may be expressed in terms of rapid changes in, for example, pH, lactic acid, glucose, and temperature [17].

The physiology of the preterm and full-term neonate is characterized by a high metabolic rate and oxygen demand (two- to three-fold increase compared with adults), which may be compromised at times of stress because of limited cardiac and respiratory reserve. The myocardium in the neonate is immature: contractile tissue constitutes only 30% of the myocardial mass, compared with 60% in mature myocardium. In addition, neonates have a lower velocity of shortening, a diminished length–tension relationship, and a reduced ability to respond to afterload stress [18, 19]. Because the compliance of the myocardium is reduced, the stroke volume is relatively fixed, cardiac output is heart rate-dependent, and the Frank–Starling relationship is functional only within a narrow range of left ventricular end-diastolic pressure compared with the mature myocardium. The cytoplasmic reticulum and T-tubular system are underdeveloped, and the neonatal heart is dependent on the trans-sarcolemmal flux of extracellular calcium both to initiate and sustain contraction. It is important to note that much of this information is derived from animal data.

Cardiorespiratory interactions are important in neonates and infants. In simple terms, ventricular interdependence refers to the fact that a relative increase in ventricular end-diastolic volume and pressure causes a shift of the ventricular septum and diminishes the diastolic compliance of the opposing ventricle [20]. This effect is particularly prominent in the

immature myocardium. Therefore, a volume load from an intracardiac shunt or valve regurgitation, and a pressure load from ventricular outflow obstruction or increased vascular resistance, may lead to biventricular dysfunction. For example, in neonates with tetralogy of Fallot and severe outflow obstruction, hypertrophy of the ventricular septum may contribute to diastolic dysfunction of the left ventricle and an increase in end-diastolic pressure. This does not improve immediately after repair in the neonate as it takes some time for the myocardium to remodel. A persistent volume load to the left ventricle following surgery, such as from a residual ventricular septal defect (VSD), may further exacerbate this situation.

The mechanical disadvantage of an increased chest wall compliance and reliance on the diaphragm as the main muscle of respiration limits ventilatory capacity in the neonate. The diaphragm and intercostal muscles have fewer type I muscle fibers (slow-contracting, high-oxidative fibers for sustained activity) and this contributes to early fatigue when the work of breathing is increased. In the newborn, only 25% of fibers in the diaphragm are type I, reaching a mature proportion of 55% by 8–9 months of age [21]. The diaphragmatic function may be significantly compromised by raised intra-abdominal pressure such as from gastric distension, hepatic congestion, and ascites.

The tidal volume of full-term neonates is between 4 and 6 mL/kg and, because of the above mechanical limitations, minute ventilation is dependent on respiratory rate. The resting respiratory rate of the newborn infant is between 30 and 40 breaths/min, which provides the optimal alveolar ventilation to overcome the work of breathing and match the compliance and resistance of the respiratory system. When the work of breathing increases, such as with parenchymal lung disease, airway obstruction, cardiac failure, or increased pulmonary blood flow, a larger proportion of total energy expenditure is required to maintain adequate ventilation. Infants, therefore, fatigue readily and fail to thrive.

The neonate has a reduced functional residual capacity (FRC); FRC is determined by the balance between the chest wall and lung compliance. Closing capacity is increased in newborns with airway closure occurring during normal tidal ventilation [22]. Neonates have reduced oxygen reserve, and in conjunction with the increased basal metabolic rate and oxygen consumption that is two to three times adult levels, are at risk for hypoxemia. Atelectasis and hypoxemia do not occur in the healthy neonate because FRC is maintained by dynamic factors including tachypnea, breath stacking (early inspiration), expiratory breaking (expiratory flow interrupted before zero flow occurs), and from laryngeal breaking (auto positive end-expiratory pressure). The propensity of the neonatal capillary system to leak fluid out of the intravascular space is especially pronounced in the neonatal lung [23], in which the pulmonary vascular bed is almost fully recruited at rest and the increases in lymphatic flow required to handle elevated mean capillary pressures (due to augmented pulmonary blood flow) are limited [24].

The glomerular filtration rate is generally low at birth but normalizes over the first few months of life. Urinary sodium excretion increases slowly during the first 2 years of life, and the inability of immature kidneys to concentrate urine and to excrete acute water and sodium loads makes fluid management in neonates, especially preterm infants, difficult. Urinary acidification capability is limited in neonates and the bicarbonate threshold is reduced. Thus, premature infants have decreased serum bicarbonate levels and lower serum pH (a non-anion gap acidosis). Neonates tolerate fluid restriction poorly, so fasting should be kept to a minimum and intravenous (IV) fluid started early; however, excessive fluid administration (as after CPB) is also poorly tolerated.

Drug pharmacodynamics and kinetics may be different in the newborn because of immature hepatic and renal function. In addition to altered drug metabolism, protein binding and clearance, the drug volume of distribution is affected by the increase in total body water of the neonate compared with the older patient. The dosing of drugs that mainly depends on renal excretion will have to be reduced and, if possible, the plasma concentration should be closely assessed to avoid accumulation and side effects. Larger doses of furosemide are needed to induce diuresis in neonates compared with adults.

The caloric requirement for neonates, especially preterm neonates, is high (100–150 kcal/kg/24 hours) [25]. Supplying adequate nutrition can be a difficult task, especially if the total amount of fluid, administered either parenterally or enterally, must be restricted, as is the case in premature neonates with CHD. Hyperosmolar feedings have been associated with an increased risk of necrotizing enterocolitis (NEC) in the preterm neonate or in the full-term neonate who has decreased splanchnic blood flow of any cause (e.g., left-sided obstructive lesions).

KEY POINTS: LIMITED PHYSIOLOGIC RESERVE

- The immature myocardium has fewer contractile elements, poor compliance, fixed stroke volume, heart rate-dependent cardiac output, and an immature T-tubular system.
- There is also ventricular interdependence.
- Limited ventilatory capacity results in early respiratory muscle fatigue. Closing capacity is increased.
- Immature hepatic and renal function leads to altered drug pharmacokinetics and pharmacodynamics.
- There is a high metabolic demand (100–150 kcal/kg/day) and oxygen demand (6–8 mL/kg/min).

Stress response

In general terms, the "stress response" is a systemic reaction to injury, with hemodynamic, endocrinologic, and immunologic effects (Box 19.2). Stress and adverse postoperative outcomes have been linked in critically ill newborns and infants. This is not surprising given their precarious balance of limited metabolic reserve and increased resting energy demand. Metabolic derangements, such as altered glucose homeostasis, acidosis, salt and water retention, and a catabolic state contributing to protein breakdown and lipolysis, are commonly seen following major stress in sick neonates and infants [17]. This complex of maladaptive processes may be associated with prolonged mechanical ventilation and intensive care unit (ICU) stay as well as with increased morbidity and mortality.

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Box 19.2: Systemic response to injury

Autonomic nervous system activation
- Catecholamine release
- Hypertension, tachycardia, vasoconstriction

Endocrine response
- Anterior pituitary: ↑ ACTH, GH
- Posterior pituitary: ↑ vasopressin
- Adrenal cortex: ↑ cortisol, aldosterone
- Pancreas: ↑ glucagon, insulin resistance
- Thyroid: ↓/→ $T_{4/3}$

Metabolic response
- Protein catabolism
- Lipolysis
- Glycogenolysis/gluconeogenesis
- Hyperglycemia
- Salt and water retention

Immunologic responses
- Cytokine production
- Acute-phase response
- Granulocytosis

ACTH, adrenocorticotropic hormone; GH, growth hormone; T_4, thyroxine; T_3, triiodothyronine.

The neuroendocrine stress response is activated by afferent neuronal impulses from the site of injury, traveling via sensory nerves through the dorsal root of the spinal cord to the medulla and hypothalamus. Anesthesia can therefore have a substantial modulating effect on this neuroendocrine pathway by virtue of providing analgesia and loss of consciousness. Outcomes after major surgery in neonates and infants may be improved when the stress response is attenuated. This was initially reported in two controlled, randomized trials comparing N_2O/O_2/curare anesthesia with or without fentanyl in neonates undergoing patent ductus arteriosus (PDA) ligation [17], and with or without halothane in neonates undergoing general surgery [26]. Fentanyl doses as low as 10 μg/kg may be sufficient for effective baseline anesthesia in neonates, although larger doses are necessary for prolonged anesthesia [27].

It is important to distinguish between suppression of the endocrine response and attenuation of hemodynamic response to stress. Because of their direct effects on the myocardium and vascular tone, anesthetic agents can readily suppress the hemodynamic side-effects of the endocrine stress response. However, the postoperative consequences of the endocrine stress response, in particular fluid retention and increased catabolism, remain unabated. Relying on hemodynamic variables to assess the level of "stress" is therefore often inaccurate. Metabolic indices such as hyperglycemia and lactic acidosis are also indirect markers of "stress", particularly as they are influenced by other factors such as cardiac output and catecholamine levels.

The effect of surgical stress has been specifically evaluated in neonates and infants undergoing cardiac surgery. Wood et al. first demonstrated a substantial increase in epinephrine and norepinephrine levels in response to profound hypothermia and circulatory arrest in infants [28]. The hormonal and metabolic response was further characterized by Anand et al. and noted such response to be more extreme and distinct from that seen in adults [29]. In addition to an increase in catecholamine, glucagon, endorphin, and insulin levels, hyperglycemia and hyperlactatemia persisted into the postoperative period. In an important subsequent study, Anand and Hickey compared a high dose sufentanil technique with halothane/morphine anesthesia in 45 neonates undergoing cardiac surgery and deep hypothermic CPB [30]. They reported a significant attenuation of hormonal and metabolic responses to surgery and bypass in the sufentanil group, with less postoperative morbidity and mortality. A conclusion from these studies supported the notion that reducing the stress response with high-dose opioid anesthesia and extending this into the immediate postoperative period is important to reduce the morbidity and mortality associated with congenital heart surgery in neonates.

These studies were performed over two decades ago. During the intervening period, there have been substantial changes in the perioperative care of infants with heart disease as well as in the management of CPB in general; along with these changes, outcomes have considerably improved. Changes in surgical practice, especially the timing of surgery, have altered the perioperative course of numerous defects and reduced the incidence of certain pathophysiologic consequences. Currently, it is less likely to see neonates in the immediate post-bypass period with extensive peripheral edema, anasarca, or other associated complications such as impaired ventricular function, reactive pulmonary hypertension, and substantial alterations in lung compliance and airway resistance. For example, just one or two decades ago, postoperative pulmonary hypertensive crises were relatively common events in infants who had been exposed to weeks or months of high pulmonary pressure and flow, such as truncus arteriosus, complete atrioventricular canal defects, and the transposition of the great arteries with VSDs. High-dose opioids were an important management component for patients at risk for pulmonary hypertensive crises. In current practice, however, these patients are operated upon at an earlier age and are therefore less likely to have significant or irreversible changes in the pulmonary vascular bed. Consequently, a strategy of high-dose opioid anesthesia to blunt the stress response may be a less critical determinant of outcome.

Further, it has been well demonstrated that high-dose opioid anesthetic techniques do not consistently block the endocrine stress response to cardiac surgery. The dose of sufentanil used by Anand and Hickey was extremely high and difficult to translate to the more common practice of fentanyl-based anesthesia. More recent studies in neonates, infants, and older children undergoing cardiac surgery have demonstrated attenuation of the pre-bypass endocrine and hemodynamic response to surgical stimulation with a variety of anesthetic techniques. These studies have included high-dose fentanyl (50 μg/kg) either by bolus or infusion [31, 32], high-dose bolus fentanyl (25–150 μg/kg) with or without low-dose isoflurane [33], remifentanil infusions at various rates (0.25–5 μg/kg/min) [34], and more recently low-dose fentanyl (10-25 μg/kg) with dexmedetomidine [35, 36]. Based upon the lack of significant stress responses reported in these studies, it is reasonable to conclude that there was appropriate neuraxial inhibition in these patients and that they were adequately anesthetized during the surgery. It is not possible to conclude, however, that one technique is superior to

another. No specific dose-response between plasma opioid level and level of hormone or metabolic stress response has been established, nor has a specific benefit been demonstrated for the method or route of opioid administration, i.e., bolus or continuous infusion.

The use of lower doses of opioids may reduce the duration of mechanical ventilation and ICU length of stay by avoiding the resulting respiratory depression from a high-dose opioid technique [37]. Recent studies have described successful early extubation of neonates undergoing heart surgery involving CPB with general anesthesia using low-dose fentanyl, volatile anesthetic agent and dexmedetomidine, administered as a continuous infusion without loading [37–39].

KEY POINTS: STRESS RESPONSE

- Systemic response to injury from surgical trauma includes autonomic nervous system activation, endocrine, metabolic and immunologic effects
- Can be associated with prolonged mechanical ventilation, ICU stay, and increased morbidity and mortality
- High dose opioid strategies do not consistently block neuroendocrine stress response during bypass but remain the main component of anesthetic management of neonates undergoing cardiac surgery

Systemic inflammatory response to CPB

Besides the surgical stimulus, additional factors contributing to the stress response include the effects of CPB, i.e., hypothermia, contact activation, hemodilution, and non-pulsatile flow [40–42]. It is well recognized that the exposure of blood elements to the non-endothelial surfaces of the CPB circuit, along with ischemia–reperfusion injury, induces a systemic inflammatory response with activation of numerous signaling cascades including complement, thrombotic, fibrinolytic, proinflammatory cytokine and oxygen-free radical pathways. These effects are magnified in neonates due to the higher bypass circuit surface area and priming volume relative to patient blood volume.

Cytokines stimulate the production of acute-phase proteins in the liver (i.e., C-reactive protein, fibrinogen, α_2-macroglobulin, and other anti-proteinases), stimulate the adhesion molecule cascade, increase protein catabolism, and augment the release of adrenocorticotropic hormone from the anterior pituitary [43, 44]. In contrast to the effect of anesthesia in the pre-bypass phase, anesthesia techniques have not been demonstrated to consistently obtund the stress responses to bypass [30, 32, 45]. This is primarily because CPB introduces a second mechanism for triggering the stress response independent of surgical stimulation. The inflammatory response and its clinical manifestation are even more pronounced in very LBW and premature newborns, in part due to the immaturity of the responding systems, low receptor density, and low vascular tone. The immature myocardium is more vulnerable to reactive oxygen species due to developmental differences compared to the adult heart, and additionally because of depleted antioxidant reserve in those with cyanotic heart disease [46].

The endothelial glycocalyx plays a key role in vascular integrity. The glycocalyx is vulnerable to several perioperative insults including ischemia-reperfusion, inflammation, and hypervolemia. Shedding of the glycocalyx in infants undergoing CPB is increased following aortic clamping (ischemia of the heart and lungs) and greatest with global ischemia during deep hypothermic circulatory arrest (DHCA) [47]. Diminution of the endothelial glycocalyx increases capillary permeability to water, solutes, and colloids, leading to tissue edema and potential multi-organ dysfunction. Total lung water is increased with an associated decrease in lung compliance and an increase in the alveolar-to-arterial O_2 gradient. Myocardial edema leads to impaired ventricular systolic and diastolic function. A secondary fall in cardiac output by 20–30% is common in neonates in the first 6–12 hours following surgery, contributing to decreased renal function and oliguria [48]. Sternal closure may need to be delayed due to mediastinal edema and associated cardiorespiratory compromise when the closure is attempted. Ascites, hepatic congestion, and bowel edema may affect mechanical ventilation, cause ileus, and delay feeding.

In recent years, numerous strategies have evolved to limit the effect of the endothelial injury resulting from the systemic inflammatory response to CPB. Significant advances in circuit miniaturization and reducing blood-contacting surfaces have been made [49]. A variety of anti-inflammatory treatment modalities have been studied, including leukocyte depletion, neutrophil adhesion blockade, and heparin coating of the CPB circuit to reduce complement and leukocyte activation. To date, no single treatment has been shown to attenuate the endothelial reaction and clinical response following CPB in neonates and infants. The most important strategy remains limiting both the time spent on bypass and the use of DHCA. This is clearly dependent, however, upon surgical expertise, experience, and patient anatomy and size. Recent advances in perfusion technology allow lower body perfusion during arch reconstruction by direct cannulation of the innominate artery and descending aorta with the full flow at mild hypothermia. These techniques should reduce splanchnic and renal ischemia-reperfusion injury; however, further clinical research is needed to demonstrate improved patient outcomes [50].

Attenuation of the stress response with deep anesthesia and hypothermia, the use of antioxidants such as mannitol, perioperative treatment with anti-inflammatory agents such as corticosteroids, adjustments in prime composition to maintain hematocrit and oncotic pressures, and finally ultrafiltration during rewarming or immediately after bypass are all attempts to further limit the clinical consequences of the inflammatory response. Corticosteroids are routinely given to infants undergoing cardiac surgery with CPB to ameliorate the inflammatory response but are of uncertain benefit [51]. In a recent multicenter trial, 1 mg/kg of dexamethasone after anesthesia induction was found to have little or no effect on mortality or major complication among 394 randomized infants (median age, 6 months) undergoing cardiac surgery with CPB [52]. A larger placebo-controlled study is currently enrolling 1,200 infants to investigate the safety and efficacy of methylprednisolone administered into the CPB pump prime [53].

Conventional CPB delivers hyperoxic perfusion. Normoxic management of CPB may reduce oxidative stress, particularly in cyanotic infants [54]. The addition of nitric oxide to

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sweep gas during CPB may have a myocardial protective effect following ischemia-reperfusion. A randomized controlled trial showed a lower incidence of low cardiac output state with the delivery of nitric oxide to the CPB circuit, with the benefit most marked in children less than 6 weeks of age [55]. Multicenter trials of these interventions delivered individually or in combination are needed to confirm improvements in clinical outcomes, whilst accounting for significant inter- and intra-hospital heterogeneity in practice [56].

An increase in glucagon levels, insulin resistance, and steroid administration may contribute to significant hyperglycemia following bypass in neonates. Tight glycemic control can be achieved with a low hypoglycemia rate after cardiac surgery in children, but it does not significantly change the infection rate, mortality, length of stay, or neurodevelopmental outcome, as compared with standard care [57, 58]. The use of insulin must be undertaken with caution, and frequent measurement of glucose levels is essential because of the risk of unintended hypoglycemia. In addition to the activation of stress hormones during CPB, triiodothyronine (T_3) levels have been shown to be low in neonates after CPB and may remain low for up to 48 hours after surgery, particularly if a sick euthyroid state develops and there is decreased conversion of thyroxine to the active T_3 in peripheral tissues [59].

Hemofiltration has become a technique commonly used to hemoconcentrate and possibly remove inflammatory mediators (complement, endotoxin, and cytokines) during or after CPB [60–63]. Hemofiltration techniques include "modified ultrafiltration" whereby the patient's blood volume is filtered after completion of the bypass, "conventional hemofiltration" whereby both the patient and circuit are filtered during rewarming on bypass, and "zero-balance ultrafiltration" in which high-volume ultrafiltration essentially washes the patient and circuit blood volumes during the rewarming process [64]. High flow rates during modified ultrafiltration have been shown to transiently decrease the cerebral circulation in young infants compared with lower blood flow rates; this could be important in newborns after CPB who may have altered cerebral autoregulation [65].

Early clinical experience suggested improved systolic and diastolic pressures after modified ultrafiltration, as well as improved pulmonary function with reductions noted in PVR and total lung water [60, 61]. While modified ultrafiltration post-bypass has been shown to improve early hemodynamic and pulmonary function, the initial increase in pulmonary compliance may not be sustained beyond the immediate post-ultrafiltration period [66]. These techniques are useful to hemoconcentrate and remove total body water, but they do not prevent the inflammatory response. The advantages of hemofiltration may be less relevant with developments in CPB circuit miniaturization [67].

Peritoneal dialysis has been recommended to treat total body fluid overload, particularly during low output states following infant cardiac surgery. Recent studies have reported successful prevention of fluid overload with continuous peritoneal dialysis, without significant morbidity and hemodynamic effects [68, 69]. In addition to decompressing the abdomen, which may, in turn, improve respiratory mechanics and requirements for mechanical ventilation, peritoneal dialysis also assists with postoperative fluid balance and may have the potential benefit of removing proinflammatory cytokines [70].

KEY POINTS: SYSTEMIC INFLAMMATORY RESPONSE TO CPB

- It is triggered by exposure of blood elements to non-endothelial surfaces of the bypass circuit.
- There is an activation of numerous signaling cascades: complement, thrombosis, fibrinolysis, cytokines, and oxygen-free radical pathways.
- There is an exaggerated response in neonates due to relatively large CPB circuit surface and prime volume as well as immature organ systems.
- Clinical manifestations are increased lung water, decreased lung compliance, capillary leak, myocardial edema and decreased cardiac output, bowel edema, and ascites.
- There are various preventive strategies, but no single treatment has proven to be fully effective yet. Strategies include limiting bypass and DHCA times, attenuation of the stress response, corticosteroids, antioxidants, ultrafiltration, and peritoneal dialysis.

Neurologic injury

Neurodevelopmental and behavioral disabilities remain prevalent in survivors after neonatal congenital heart surgery. The etiology is multifactorial regarding timing and mechanisms. Brain magnetic resonance imaging (MRI) data performed both before and after newborn cardiac surgery using hypothermic bypass demonstrates a disturbing incidence of white matter injury and the development of periventricular leukomalacia (PVL) [71–79]. Pathogenesis of PVL in premature infants relates to three interacting factors. There is an incomplete development of the vascular supply of the cerebral white matter, impairment in cerebral blood flow regulation, and thirdly, the maturation-dependent vulnerability of the oligodendroglial precursor cell to ischemia-reperfusion injury [80]. Term neonates with CHD may share similar vulnerabilities to white matter injury with hypoxia/ischemia. Elevations of brain lactate on MR spectroscopy, indicating impaired cerebral metabolism, are found in over half of patients with CHD before neonatal surgery [81]. In neonates with transposition of the great arteries, preoperative brain injury is associated with hypoxemia and a longer time to surgery [71].

Adverse neurological outcomes are multifactorial after bypass and may be secondary to the duration of CPB [82, 83], rate and depth of cooling [84–86], perfusion flow rate [87], duration of circulatory arrest, pH management on bypass [10], hematocrit [11, 88–90], and embolic events. Strategies to optimize cerebral protection during deep hypothermic bypass, with or without circulatory arrest, include longer duration of cooling (>20 minutes), the use of the pH-stat strategy of blood gas management (addition of CO_2 to the oxygenator), and maintenance of a higher hematocrit (>25%) [91, 92].

Deep hypothermia (≤18 °C) with circulatory arrest or antegrade cerebral perfusion may be necessary for selected neonates undergoing cardiac surgery to facilitate the surgical procedure, e.g., reconstruction of the aortic arch. In the past, DHCA was associated with a high incidence of obvious neurological injury manifesting as postoperative seizure activity

and choreoathetosis. While there may be no optimal "safe" duration of DHCA, the accepted limit has been reduced over the years from approximately 60 minutes to 30 minutes at temperatures <20°C [12, 93]. Multiple studies have compared neurological outcomes in neonates undergoing aortic arch reconstruction using either DHCA or antegrade cerebral perfusion and found no difference in neurodevelopmental outcome or new postoperative MRI injury [93–98]. It remains debatable whether more prolonged use of antegrade cerebral perfusion is as safe as a short run of DHCA.

The risk of brain injury in newborns is clear and supports the use of routine perioperative neurologic monitoring with technology such as near-infrared spectroscopy (NIRS), transcranial Doppler assessment of cerebral blood flow velocity, and continuous EEG [91, 99, 100]. Multiple studies of infants undergoing cardiac surgery have found associations between diminished cerebral oxygen delivery, as indicated by NIRS monitoring, and worse neurodevelopmental outcome and/or increased white matter injury on MRI [101–103]. Yet prospective studies on the effects of interventions in response to low cerebral oximetry measurements on neurologic outcomes are lacking.

With improvements in neurologic protection over recent years, the incidence of perioperative clinical seizures has declined substantially. However, subclinical seizures remain common with as many as 7% of postoperative neonates experiencing electroencephalographic only seizures (69% focal; 62% electrographic status epilepticus) [104]. Recognition of the incidence of subclinical seizures has led to increasing consensus on the benefit of routine use of continuous EEG monitoring after neonatal cardiac surgery. Data demonstrating a beneficial effect of aggressive management of perioperative electrographic seizures on long-term neurodevelopment outcomes are lacking.

Given the known risks associated with complex CHD, regular neurodevelopmental assessment throughout childhood and targeted multidisciplinary therapy are critical to optimizing outcomes and quality of life of patients [105]. The plasticity of the immature nervous system is such that it responds well to well-timed, family-centered high-quality early intervention [106, 107]. See Chapter 14 for an extensive discussion of neurological monitoring, risk factors, and outcomes.

KEY POINTS: NEUROLOGICAL INJURY

- Long-term neurodevelopment is an important outcome marker for pediatric cardiac surgery.
- The causes of neurological injury are multifactorial; it can happen *in utero*, as pre-, intra-, and post-operative events, or as a result of CPB management strategy.
- There is no "safe" duration of DHCA, and the accepted limit is now ~30 minutes at <20 °C.
- Cerebral protection during DHCA involves slow cooling (>20 minutes), higher hematocrit (>25%), and pH-stat management.
- There has been a change in practice toward antegrade cerebral perfusion as an alternative to DHCA.

Premature infants and low birth weight neonates

For term newborns with a weight >2.5 kg, positive outcomes after cardiac surgery and CPB are well established, and early complete repair is currently considered the standard of care. More recently, the improving survival of premature and LBW neonates has added a new dimension to the management of CHD. Although the technical aspects of CPB in small neonates are challenging, recent surgical advances allow routine corrective repair of complex heart disease in neonates weighing less than 2,000 g. In our experience, neither gestational age nor patient size precludes successful complete repair of lesions such as tetralogy of Fallot, truncus arteriosus, and transposition of the great arteries.

In addition to the physiologic limitations previously described for any newborn, the effects of the underlying cardiac disease and the implications of the surgical interventions, typical complications of prematurity must be considered. The management of respiratory distress syndrome, fluid overload, NEC, and intraventricular hemorrhage can be extremely challenging in premature babies with CHD. Many of these complications can influence the timing and achievability of complete surgical repairs. Even with technically successful repairs in premature and LBW neonates, the effects on future development and the potential need for re-interventions have not been established and will require further investigations and long-term follow-up [108, 109]. Table 19.2 summarizes the major challenges in the perioperative management of premature infant [110].

Pulmonary function

The immature airway and lungs of premature and very LBW neonates predispose them to hypoxia and ventilation difficulties. Lung compliance is reduced because the alveoli are primarily composed of thick-walled saccular spaces. The very compliant chest wall results in a significant mechanical disadvantage with lower FRC and O_2 reserve, and early respiratory muscle fatigue. Dead space ventilation as a proportion of tidal volume is increased. Production of surfactant begins between 23- and 24-weeks' gestation and may be inadequate until 36-weeks' gestation [111]. Respiratory distress syndrome (RDS) from surfactant deficiency results in low lung volumes and poor compliance, increased intrapulmonary shunt, and ventilation/perfusion (V/Q) mismatch, leading to severe hypoxia. Immature respiratory drive, increased pulmonary edema due to patent ductus arteriosus, pulmonary infections, ventilator-associated lung injury, atelectasis, and secondary surfactant deficiency contribute to respiratory failure [112]. Invasive ventilation and high concentration oxygen give rise to bronchopulmonary dysplasia (BPD) by inducing heterogenous lung injury with regions of atelectasis and other regions of hyperinflation, airway smooth muscle hyperplasia, interstitial fibrosis and pulmonary vascular remodeling.

With the introduction of antenatal steroids and intratracheal surfactants, both morbidity and mortality of RDS and BPD have decreased [112]. Standard of care has shifted to initial treatment with non-invasive ventilatory support in preterm infants

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Table 19.2 Physiologic challenges for management of the premature neonate with congenital heart disease

System	Physiologic challenges	Considerations for perioperative management
RDS, apnea of prematurity	• RDS may contribute to poor oxygenation. • Oxygenation goals not well defined in preterm • Permissive hypercapnia reduces BPD in preterm infants but may alter hemodynamics in CHD patient • Premature neonates at risk for apnea	• Intubation and surfactant/positive pressure ventilation may be necessary • SUPPORT trial found lower oxygenation goals reduced BPD and ROP but increased mortality. • Consider ventilator strategies utilizing permissive hypercapnia. • Utilize caffeine for apnea due to improved survival without neurodevelopmental impairment in VLBW infants. Aminophylline prevents apnea in term neonates on prostaglandin but not studied in premature neonates.
Preoperative genetic testing	• Genetic abnormalities more common in infants with CHD (especially trisomy 13, 18, 21, and 22q11.1 deletions) • DiGeorge syndrome occurs in 12% of infants with CHD; common in conotruncal lesions	• Karyotype and/or specific testing for 22q11.2 deletion (DiGeorge syndrome) may be warranted.
Neurologic Imaging	• Up to 50% with preoperative white matter injury or stroke • Risk factors are hypoxemia and time to surgery.	• Obtain early cranial ultrasound. • Preoperative MRI when indicated/feasible

without cardiorespiratory failure at birth. Less invasive surfactant administration methods show potential in improving long-term outcomes [113]. A target SpO_2 of 90-95% in infants with gestational age <28 weeks until 36 weeks' postmenstrual age is recommended based on three large clinical trials that showed a lower SpO_2 range had a greater rate of mortality [114]. The demographic profile of BPD has shifted to earlier preterm infants (<29 weeks gestational age). The effect of BPD on the outcome of cardiac surgery in the current era is unknown.

The potential for RDS is another important consideration for premature infants undergoing CPB. Lung injury post-cardiac surgery is triggered by shear forces and contact of blood with the non-endothelial surfaces of the extracorporeal circuit, resulting in activation of a systemic inflammatory response [115]. In addition, significant depletion of surfactant may occur [116], and when combined with endothelial injury, can contribute to pulmonary hypertension and altered lung compliance in the immediate postoperative period. Except for individual case reports and small single-center studies [117, 118], there are no data to support prophylactic use of surfactant, pre- or post-CPB.

Excessive pulmonary flow from certain cardiac defects will increase total lung water and prevent or delay weaning from ventilatory support in the LBW or premature newborn. Although RDS with increased PVR will limit pulmonary blood flow initially, as the lung injury resolves and the PVR decreases, pulmonary blood flow will substantially increase. For premature infants without RDS, the pulmonary vascular tone is typically low, and pulmonary blood flow may be extremely high in cardiac defects with a large left-to-right shunt, such as truncus arteriosus. Medical management with mechanical ventilation, diuretics, inotropic support, and afterload reduction is often ineffective in treating systemic hypoperfusion due to significant run-off to the pulmonary circulation. As a result, continuing conservative treatment while waiting for an appropriate weight gain is often not a reasonable option, and surgical intervention is the only alternative. Palliation with a pulmonary artery band to limit pulmonary blood flow is technically challenging in LBW or premature newborns, and subsequent distortion of the pulmonary arteries may severely complicate future surgical procedures. Therefore, early complete surgical repair may be indicated to provide optimal conditions for growth and development.

A similar problem arises in cyanotic LBW or premature neonates with ductus-dependent pulmonary blood flow. A longer-term infusion of prostaglandin E_1 may be considered, but may result in unwanted inherent side-effects (apnea, edema, gastric outlet obstruction). In addition, the run-off across a large ductus is difficult to control and systemic hypoperfusion may develop. Low concentrations may be used (0.01 μg/kg/min), but a clear dose-response relationship between ductal size and PGE_1 concentration has not been demonstrated. Palliation with a modified BT shunt or ductal stent is possible, but potential problems are a distortion of the pulmonary arteries, thrombosis or stenosis and reduced pulmonary blood flow, or, on the other hand, excessive flow across the shunt, resulting in systemic hypoperfusion and cardiac failure from volume overload. Therefore, the side-effects of palliation could further impair growth and development, and the best alternative may be early surgical repair. Successful repair in LBW and premature infants with tetralogy of Fallot has been reported [119, 120]. The postoperative course of these patients is often prolonged and characterized by restrictive right ventricular physiology. Nevertheless, if complete repair has been accomplished without significant residual lesion, this early anatomic correction provides the best option for longer-term survival and growth.

Premature and LBW infants with single-ventricle physiology are difficult to manage, and an adequate balance between the ductus-dependent pulmonary or systemic flow may not be achieved. Systemic hypoperfusion (NEC, renal hypoperfusion) and feeding intolerance are commonly encountered.

In general, size limitations are a considerable problem in newborns who require stage I palliation for conditions such as HLHS. Balancing systemic and pulmonary blood flow in an LBW newborn after a Norwood operation can be challenging. The hybrid procedure is an alternative to the Norwood palliation that may be preferable in the LBW neonate. The hybrid technique is performed in the catheterization laboratory or a special angiography operating room suite. After exposure through a median sternotomy, both pulmonary arteries are banded and the patents ductus arteriosus is stented via the main pulmonary artery under fluoroscopic guidance. The hybrid procedure does not require CPB, thereby avoiding the potential cannulation problems and risk for additional neurologic injury [121, 122]. Retrospective studies suggest a survival benefit of the hybrid procedure in premature and LBW neonates, but prospective randomized studies are lacking [123–126]. A novel, nonsurgical palliation for newborns with HLHS using endoluminal pulmonary banding and duct stenting has recently been described [127].

KEY POINTS: PULMONARY FUNCTION IN PREMATURE AND VERY LBW NEONATES

- There is a mechanical disadvantage (reduced lung compliance, increased chest wall compliance, low FRC), surfactant deficiency, increased V/Q mismatch, and early fatigue of respiratory muscles.
- BPD and RDS may complicate management and preclude early extubation.
- There is pulmonary edema and increased work of breathing due to increased pulmonary blood flow with certain types of CHD.

Cardiac function

Fetal cardiac myocytes are morphologically different from those of adults. The fetal myocyte is smaller, has only one nucleus and fewer myofibrils, which are less well organized [128]. In the third trimester, a period of rapid cardiac growth, primarily driven by cardiomyocyte hyperplasia occurs. Birth results in a switch in the growth of the myocardium from the fetal hyperplastic to the adult hypertrophic pattern [128]. Preterm birth necessitates abnormal myocyte hypertrophy to achieve a normal postnatal cardiac mass [129]. At birth, the preterm heart tends to be more globular. Clinically stable preterm infants have a normal left ventricular systolic function but altered diastolic function, with greater dependence on atrial contraction [130, 131]. Echocardiography data suggests the left ventricular systolic performance in premature infants during early life is preserved in the setting of a lower afterload [132]. Altered diastolic dysfunction persists at 3 months of age in preterm infants [129]. The morphological and functional cardiac impairments in individuals born preterm are apparent in neonatal life persist across childhood and into young adulthood [133]. This population may be more vulnerable to cardiovascular disease as they age [134].

Necrotizing enterocolitis

CHD is an important predisposing factor for developing NEC [135]. The incidence of NEC in neonates undergoing cardiac surgery is around 2-4% [136–138]. Epidemiologic evidence suggests that the most common form of NEC in the premature neonate is triggered by inflammatory and microbial processes and not by a preceding ischemic event [139]. In contrast, NEC in term infants with CHD appears to be a clinically distinct entity and is due primarily to intestinal ischemic injury [135, 139]. CHD lesions with the highest risk of NEC are those with significant systemic to pulmonary circulation runoff, specifically HLHS, aortopulmonary window, truncus arteriosus, and patients with episodes of poor systemic perfusion [137]. Persistent diastolic flow reversal in the abdominal aortic Doppler profile is associated with an increased risk of NEC in term infants with CHD [140].

Clinical signs of NEC include abdominal distension, feeding intolerance, temperature, and glucose instability, hemepositive or frank blood in the stool, abdominal guarding, and tenderness. Abdominal radiographic examinations may demonstrate distension or an abnormal gas pattern, pneumatosis, portal venous gas, or intraperitoneal air consistent with perforation. Thrombocytopenia and leukocytosis are usually evident on blood examination. If NEC results in perforation or severe bowel ischemia, the neonate may develop sepsis with hypotension, capillary leak, poor perfusion, and edema. On most occasions, patients can be treated medically with antibiotics, vasoactive support, and parenteral nutrition; less frequently, laparotomy and bowel resection may be necessary [141, 142]. The key to management is to improve perfusion and O_2 delivery to the splanchnic system. Therefore, once hemodynamically stable without clinical signs of sepsis, early cardiac surgical intervention to improve splanchnic perfusion is preferable. In a single-center retrospective study, Cheng et al. found patients with proven NEC (without perforation) who underwent early cardiac surgery had a higher survival rate than those managed medically and with delayed surgery (75% vs. 44%) [143].

NEC is associated with increased hospital length of stay, worse neurodevelopmental outcomes and higher mortality [136, 144, 145]. Recent research has focused on earlier recognition and risk stratification. Splanchnic NIRS and biomarkers, such as intestinal fatty acid-binding protein, show early promise [146–148]. Little evidence exists to guide safe feeding and considerable variation exists in feeding practices, particularly in neonates with duct-dependent lesions. Unfortified human milk feeding and standardized feeding protocols may reduce the risk of NEC.

KEY POINTS: NECROTIZING ENTEROCOLITIS

- There is an increased frequency of NEC in patients with CHD, with a run-off to the pulmonary circulation and poor systemic perfusion leading to mesenteric ischemia.
- NEC is associated with increased mortality and prolonged hospitalization.
- Early cardiac surgery in a patient with proven NEC can improve survival.

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Intraventricular hemorrhage

Intraventricular hemorrhage (IVH) results from bleeding into the lateral ventricle following rupture of fragile microvessels within the subependymal germinal matrix [149]. The risk of intraventricular hemorrhage (IVH) decreases with increasing gestational age. The incidence of severe IVH (grade 3 and 4) from a NICHD Neonatal Research Network study was 38%, 26%, and 7% of infants born at 22, 24, and 28 weeks of gestation, respectively [150]. Antenatal corticosteroids and delayed cord clamping decrease the risk [151, 152]. Nearly all cases of IVH in preterm infants occur within the first 5 days of postnatal life [153]. Morbidity due to IVH is related to severity grade. Grade 1 and 2 IVH generally have a favorable prognosis, whilst up to 60% of infants with grade 3 or 4 IVH develop cerebral palsy or cognitive delay [154, 155]. Post-hemorrhagic hydrocephalus complicates 1%, 4%, 25% and 28% of cases of grades 1 through 4 IVH, respectively [156].

The pathogenesis relates to developmental immaturity of the germinal matrix and impairment of cerebral autoregulation [157, 158]. The fragility of the thin-walled capillaries makes them more prone to rupture spontaneously or because of inadequate cerebral autoregulation to stressors, such as hypoxia, hypercarbia, or hypotension [158]. There are no prospective data suggesting an increased risk for IVH in LBW infants if they undergo early repair and CPB [159, 160]. Nevertheless, there is increasing data from MRI examinations of the newborn brain in the perioperative period that support the notion that the immature brain is vulnerable to injury related to cardiac surgery and CPB, particularly in watershed distributions [81, 161, 162]. It is unknown whether the premature or LBW neonate has an even higher risk.

The diagnosis of IVH before surgery is important, because of the potential for extension of the hemorrhage with surgical stress, CPB, anticoagulation and changes in blood pressure. As a baseline, we routinely perform a cranial ultrasound in all premature (<35 weeks' gestation) neonates prior to cardiac surgery. There are no clear guidelines regarding the management of premature neonates with IVH prior to surgery. Delaying surgery is prudent to lower the risk of extension of the bleed and additional neurologic injury. This may not be possible for all defects; however, in general, our practice is to wait approximately 7–10 days before undergoing surgery with CPB.

KEY POINTS: INTRAVENTRICULAR HEMORRHAGE IN PREMATURE AND VERY LBW NEONATES

- Risk of IVH decreases with increasing gestational age.
- IVH in the premature infant results from the immaturity of the germinal matrix blood vessels and impairment of cerebral autoregulation.
- There is concern regarding the expansion of preexisting IVH with surgical stress, CPB, anticoagulation, increased fibrinolytic activity and sudden changes in cerebral perfusion pressure.
- Preoperative cranial ultrasound in premature neonates is recommended.

Outcome after congenital heart surgery

Several early studies evaluated the overall outcome of preterm and very LBW infants undergoing congenital heart surgery [119, 120, 159, 163–166]. Prematurity and low birth weight were shown to be independent risk factors for increased morbidity and mortality. Data from the Society of Thoracic Surgeons Congenital Heart Surgery Database showed significantly increased operative mortality in infants weighing less than 2.5 kg compared with infants weighing 2.5–4 kg following both two-ventricle repairs and single-ventricle palliation [163]. Lower weight at the time of surgery remained strongly associated with mortality risk after stratifying the population by Risk Adjustment for Congenital Heart Surgery (RACHS) score and Aristotle Basic Complexity levels. More recent data have shown mortality rates have remained higher for LBW infants than for normal-weight infants, even after considering the effects of confounders [109, 167–171].

Hickey et al. found that in infants requiring cardiac intervention, the relationship between birthweight and survival is non-linear with an inflection point at 2.0 kg, below which there is a marked decline in survival [109]. Increasingly, surgeons have moved toward 2.0 kg as the cut-off to define low weight for cardiac surgery. Low birthweight infants are at a higher risk of death, even in the absence of CHD. Anderson et al. used epidemiologic modeling to describe the additive risk of performing cardiac surgery in 118 neonates with birth weight ≤2.0 kg after accounting for baseline risks of low birth weight [168]. Cardiac surgery was estimated to increase the risk of mortality by around 10% when compared to similar-weight infants not requiring surgery. Approximately half of the risk of mortality in the low-weight surgical cohort could be explained by the infant's birth weight alone.

It is difficult to separate out the impact of preterm birth from LBW on outcome in neonates born with a congenital heart defect. In a single-center study that included 146 patients weighing <2.5 kg at the time of surgery, Kalfa et al. found that gestational age <36 weeks at birth was an independent risk factor for early mortality [171]. Using outcome data from the Single Ventricle Reconstruction trial, Miller et al. found that preterm delivery, but not LBW, was independently associated with an increased risk of death at age 6 years. They concluded that preterm birth and LBW, although often concomitant, are not equivalent, impacting outcomes after the Norwood procedure through mechanisms independent of perioperative course [169]. Of note, LBW was associated with worse neurodevelopment outcomes despite the similar length of stay and complications.

While it is preferable to correct congenital cardiac defects early after birth to promote normal growth and development, this may be difficult to achieve in the premature and very LBW neonate [119, 120, 159, 164]. The causes are multifactorial and include technical issues related to small cardiac structures and cannulation requirements for CPB, the immaturity of organ systems (especially the lungs, myocardium, and germinal matrix in the brain), increased risk of bleeding from coagulopathy after CPB, and an immature stress response that may increase the risk for infection and promote a catabolic state in a newborn with limited nutritional reserves. All these factors contribute directly to the increased mortality risk as well as longer duration of

mechanical ventilation, intensive care, and hospital stay for the premature and LBW newborn undergoing cardiac surgery. However, intentional delay to achieve weight gain and maturation in patients with congenital heart defects requiring intervention does not appear to improve survival rate [109].

Despite advances in surgical and CPB techniques and improved outcomes, LBW neonates remain a challenging population for both surgeons and anesthesiologists. A reasonable conclusion from the later studies described here is 2.0 kg is an important cutoff point, with LBW and premature newborns < 2.0 kg having a higher risk for mortality and morbidity regardless of the surgical procedure. In addition to size limitations, end-organ immaturity, co-morbidities, and chromosomal anomalies are important contributing factors to adverse outcomes. Careful attention to detail is essential, and optimal management requires the close collaboration of a multidisciplinary perioperative team.

KEY POINTS: OUTCOME OF CARDIAC SURGERY IN PREMATURE AND VERY LBW NEONATES

- Successful cardiac surgery can be performed in premature and very LBW neonates but with increased risk due to immaturity. There is no survival benefit with medical management and delayed surgery.
- There is increased mortality for neonates weighing ≤2.0 kg for two-ventricle repair and single-ventricle palliation.
- End-organ immaturity, type of cardiac lesion, co-morbidities, and chromosomal anomalies are all contributing factors to adverse outcomes.

Patent Ductus arteriosus occlusion in premature neonates

In recent years the availability of devices for transcatheter PDA occlusion in premature neonates has made this the approach of choice in many institutions, rather than surgical PDA ligation performed at the bedside in the neonatal ICU, or in the operating room [172, 173]. One such device is the Amplatzer Piccolo Occluder (Abbott, Abbott Park, IL) which is U.S. FDA approved for patients as small as 700 g. There are published reports of PDA occlusion in patients weighing as little as 600 g. This procedure is done via a transvenous approach with a 4 Fr sheath in the femoral vein, without any arterial access due to the high risk of occlusion in these small patients. The procedure is performed as a combination angiographic and transthoracic echocardiography (TTE) imaging approach, and a long sheath is advanced through the right atrium, right ventricle, and pulmonary artery into the PDA, where the occluder is deployed (Figure 19.1). Before deploying the device, fluoroscopy, angiography, and TTE are utilized to ensure proper placement, avoiding occlusion of the descending aorta, or branch pulmonary arteries. Although there have been no prospective controlled trials directly comparing transcatheter PDA occlusion vs. surgical PDA ligation in premature infants, retrospective comparison studies report faster improvement in respiratory function with the transcatheter approach. Case series of PDA occlusion in infants report successful occlusion rates of over 90%, with failures most often due to the encroachment of the device into the branch pulmonary arteries or descending aorta, resulting in the removal of the device and referral for surgical PDA ligation. Major complications are reported in 5-10% of infants <2 kg [174, 175]. In a report of 100 patients 700–2,000 g undergoing PDA occlusion with the Piccolo device, the success rate was 99% [176]. Five patients had worsening tricuspid regurgitation without clinical manifestations, two had intraprocedural and one postprocedural device migration, there were two cases of aortic obstruction, and two major hemorrhages and one case of hemolysis.

Anesthetic considerations include transport from the NICU to the catheterization laboratory in a heated isolette to maintain patient temperature, catheterization laboratory heated to 80° F and forced-air warming and other temperature maintenance strategies. A neonatal ventilator may be required for small patients, and a large leak around the endotracheal tube is often present. Packed red blood cells need to be available, which should be less than 7 days old or checked for K+ <8 meq/L. Arterial monitoring is not usually employed unless an arterial catheter is already present. Potential complications include severe tricuspid regurgitation with sheath passage, atrioventricular block, and device embolization. Flushing of the sheath is minimized to reduce the risk of volume overload, and heparin is typically not utilized in the flush. Pressure on the thorax or abdomen from the TTE probe may affect respiratory or hemodynamic stability in these tiny patients. There are also reports of PDA occlusion performed at the bedside with portable fluoroscopy and TTE.

Fetal cardiac intervention

Advances in fetal echocardiography have improved accuracy in the diagnosis and evaluation of CHD, which has in turn led to improved counseling and perinatal management. Studies have shown, specifically for HLHS and transposition of the great arteries, that prenatal diagnosis results in an improved preoperative condition and possibly decreased mortality [177, 178]. However, there are few studies that document the natural history of cardiac growth and physiological changes in individual fetal cardiac malformations or the timing of their impact during fetal growth. Unfortunately, there is no specific animal model of cardiac malformations that is like the human fetus to provide insights into pathophysiology and effects on development or to aid in developing management strategies. Nonetheless, we know that the normal development of the heart and great vessels in the fetus requires normal blood flow patterns. For example, changes in ventricular growth and function can be seen on serial fetal echocardiograms in a fetus with aortic or pulmonary valve stenosis [179], leading to ventricular hypoplasia, fibrosis, and often abnormalities of the coronary arteries, systemic arterial and pulmonary venous morphology [180]. In a worst-case scenario, fetal critical aortic stenosis may progress

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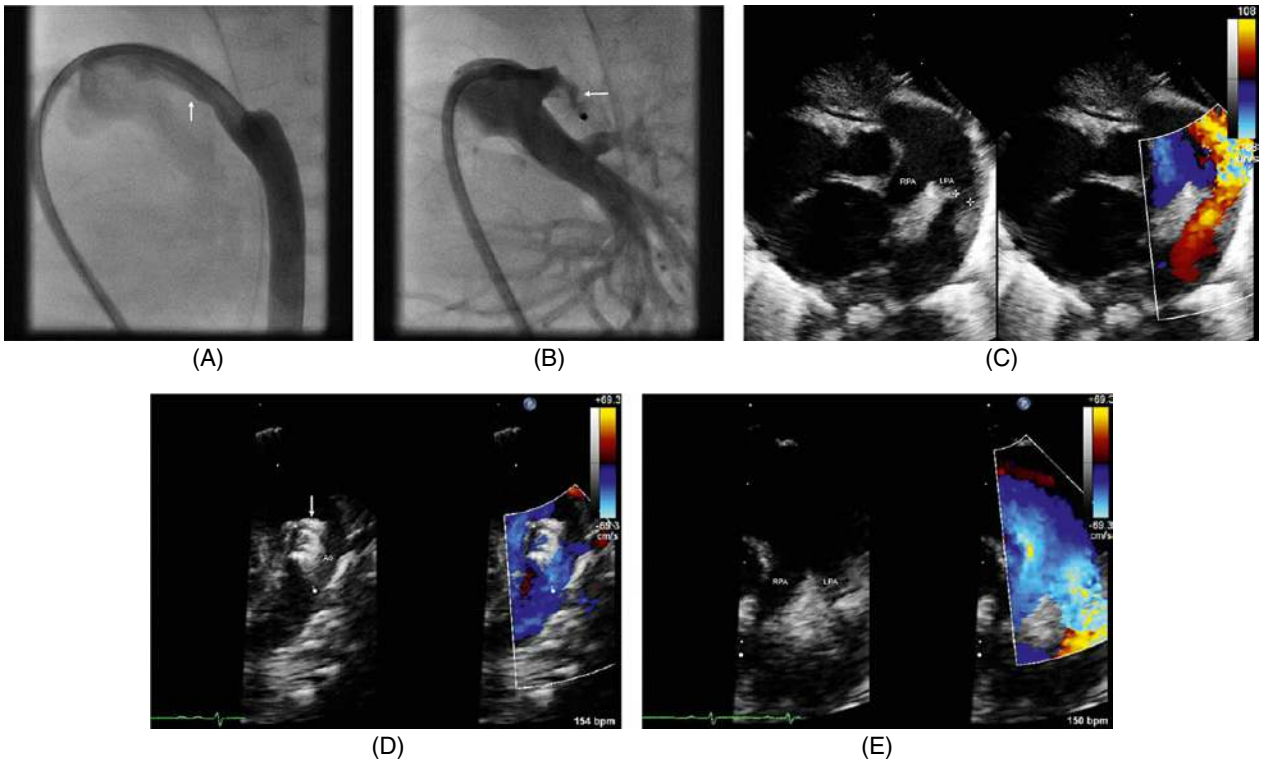


Figure 19.1 Ductus arteriosus closure in a premature infant. (A) Descending aortic angiogram through a 4-Fr-long sheath that has been advanced transvenously through the ductus arteriosus (*arrow*) of a 2-month-old, ex-30-week premature infant weighing 1.2 kg. Note that no arterial access was obtained in the patient, in order to avoid the risk of arterial trauma. (B) Angiogram in the main pulmonary artery after device positioning, but before full release showing the good position of a 4-mm AVP II device (Abbott, Abbott Park, IL) (*arrow*) in the ductus arteriosus. (C) Transthoracic echocardiography (2D and corresponding color images) performed in the cardiac catheterization laboratory before ductus arteriosus device deployment showing the large ductus arteriosus (between markers). The right pulmonary artery (RPA) and left pulmonary artery (LPA) are also visualized. (D) Transthoracic echocardiography (2D and corresponding color images) performed in the cardiac catheterization laboratory after ductus arteriosus device deployment (*arrow*) showing unobstructed flow in the descending aorta (Ao). (E) Transthoracic echocardiography (2D and corresponding color images) performed in the cardiac catheterization laboratory after ductus arteriosus device deployment showing unobstructed flow in right pulmonary artery (RPA) and left pulmonary artery (LPA). (Source: Eilers et al. [172]. Reproduced with permission from Springer Nature.)

to HLHS in a proportion of cases, resulting in univentricular circulation. One of the major reasons for interventions in the fetus, therefore, is to enhance blood flow patterns to allow for better *in utero* development of the heart and improve postnatal outcomes. This "flow theory" is based on the concept that normal flow across the foramen ovale, atrioventricular and semilunar valves contributes to normal growth of the ventricles. Obviously, other motives for FCI include improving survival in fetuses at high risk of prenatal or neonatal death and to allow recovery under the most supportive *in utero* conditions with periods of enhanced wound healing and myocyte proliferation [181, 182]. The recognition that certain CHDs can evolve *in utero* and that early intervention may improve outcomes has led to the evolution of FCIs (Table 19.3).

Transplacental pharmacotherapy of the fetus

Historically, the first FCIs were pharmacological interventions to treat fetal tachyarrhythmia or heart block. In 1975, Eibschitz et al. described the use of propranolol, given to the mother, to treat fetal ventricular tachycardia [184]. Digoxin and many other antiarrhythmic medications (sotalol, amiodarone, flecainide) followed over the years [185–189]. This transplacental pharmacotherapy is usually effective in the non-hydropic fetus. Still, fetal deaths occur in approximately 10% of all fetal arrhythmia patients, and at a higher rate in fetuses with hydrops. Fetal AV block has been treated with transplacental sympathomimetic agents and/or dexamethasone (for autoimmune-related cases) [190–193]; however, the impact on outcome is not well defined. Fetal pacing has been attempted where the fetus is too premature to be delivered and other medical therapies have failed to control heart failure and hydrops [194–196], but so far there has been no successful medium- or long-term outcome in humans.

Prenatal non-steroidal anti-inflammatory drug (NSAID) therapy has recently been described to achieve ductus arteriosus constriction and reduce circular shunt physiology in fetuses with severe Ebstein anomaly and pulmonary regurgitation [197]. Circular shunt, due to unrestricted ductal flow in presence of significant pulmonary and tricuspid regurgitation, is a major risk factor for perinatal mortality. Early results of NSAIDs are encouraging; prolonging gestation and improving survival where ductal constriction is achieved.

Table 19.3 Congenital heart conditions that can potentially be treated with fetal cardiac intervention (FCI)

Condition	Actual or possible FCI
Risk for *in utero* progression	
Fetal AS and evolving HLHS	Balloon aortic valvuloplasty
PA/IVS and evolving HRHS	Pulmonary valvuloplasty
Premature closure of PDA and pulmonary hypertension	Ductal stenting
Absent pulmonary valve with evolving bronchomalacia	Pulmonary arterioplasty and/or valvuloplasty
Risk for fetal or early neonatal death	
Fetal tachycardia with hydrops	Maternal antiarrhythmic therapy
Anomalies causing hydrops	Maternal digoxin
Congenital heart block	Maternal sympathomimetic therapy, pacemaker
Severe Ebstein malformation	Maternal NSAID therapy
Severe congenital MS with AS and intact atrial septum	Balloon aortic valvuloplasty, atrial septoplasty
HLHS with intact atrial septum	Atrial septoplasty/stenting
TAPVR with obstruction	Stenting of obstructed vertical vein

FCI, fetal cardiac intervention; AS, aortic stenosis; HLHS, hypoplastic left heart syndrome; PA, pulmonary atresia; IVS, intact ventricular septum; HRHS, hypoplastic right heart syndrome; PDA, patent ductus arteriosus; MS, mitral stenosis; TAPVR, total anomalous pulmonary venous return, NSAID, non-steroidal anti-inflammatory drug.
(Source: McElhinney et al. [183]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Open fetal cardiac interventions

Open FCIs involve surgical incisions into the uterus or access via a surgical trocar ≥3 mm in diameter as in most fetoscopic approaches. Unfortunately, incisions of this size or larger seem to be associated with an extremely high incidence of preterm labor (80%) [198]. Over the past 25 years, experimental cardiac surgery in fetal lamb and other animal models has resulted in increased knowledge of the cardiovascular and placental response to extracorporeal circulatory bypass. Fetal bypass, using the placenta as an oxygenator, leads to significant post-bypass placental dysfunction with impaired fetal gas exchange, reduction in uterine blood flow, and significant fetal stress response [199–201]. Despite many problems, these models have shown that cardiac surgery on the lamb fetus with survival to full term is technically possible. So far, open fetal heart surgery in humans has only been attempted a few times [183].

Catheter-based fetal cardiac interventions

Ultrasound-guided, percutaneous, catheter-based FCI is a technique that allows for *in utero* treatment of a small subset of CHD. The potential candidates for FCI fit into one of two categories: diseases that progress from the time of mid-gestation diagnosis to birth; and diseases that carry a high risk of demise *in utero* or perinatally [202]. To date, the main target lesions for FCI are aortic stenosis with evolving HLHS, HLHS with an intact or restrictive atrial septum, and pulmonary atresia with the intact ventricular septum (PA/IVS) with concern for worsening right ventricular hypoplasia. Careful patient selection is crucial. Currently, there is still a significant risk of fetal demise, unknown long-term outcomes, and a potential risk for the mother [202].

An FCI program must be multidisciplinary, with collaboration between neonatologists, obstetricians (specialized in prenatal diagnosis and fetal medicine), pediatric cardiologists, and anesthesiologists (fetal and obstetric) [203]. The procedures are performed in the hospital where the mother is the patient, to offer the best care for the pregnant woman. Various anesthesia techniques have been described for the management of the mother during fetal procedures, including IV sedation with local anesthesia, spinal or epidural anesthesia, general anesthesia, and combined techniques [204]. In the current era, maternal conscious sedation with epidural anesthesia or local anesthesia by injection of lidocaine along the planned needle trajectory from the skin to the uterine wall is used for FCI [203–205]. With greater awareness of the fetal stress response and pain perception [206–209], all fetuses now receive analgesia with 20–50 μg/kg fentanyl, administered intramuscularly or into the umbilical vein [210, 211]. A muscle relaxant is administered to the fetus to facilitate positioning and achieve immobility.

Monitoring of the fetus is usually limited to heart rate and basic contractility via ultrasound or echocardiography. Under continuous ultrasound guidance, a special 18- or 19-gauge cannula is passed through the maternal abdomen, uterine wall, and fetal chest wall into the fetal heart (either LV, RV or RA, depending on the procedure to be performed) (see Figure 19.2). Balloon positioning for inflation is based on external measurements and ultrasound imaging, and it is inflated when in the correct position (Figure 19.3). Procedural outcomes for FCI have improved since the procedures were initially attempted in the early 1990s, for example, the technical success rate for fetal aortic valvuloplasty is currently around 94% [203]. Intraoperative fetal cardiac complications remain common. Especially during procedures requiring

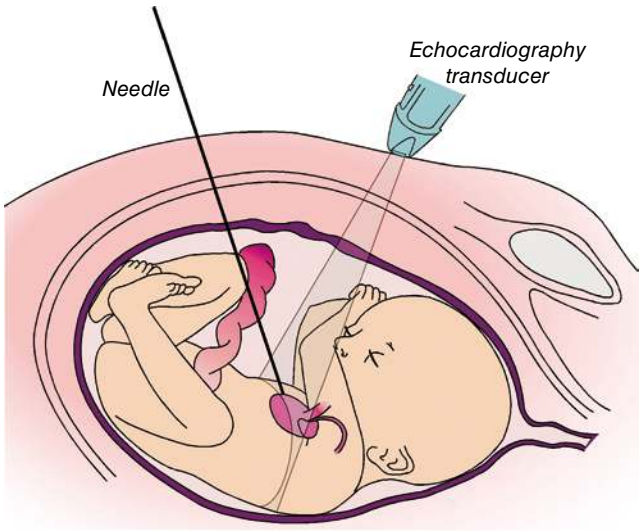


Figure 19.2 Ideal fetal position for fetal intervention. The fetal left chest is anterior and the pathway from the maternal abdomen to left ventricular apex is unobstructed. (Source: Dr. A. Marshall. Reproduced with permission.)

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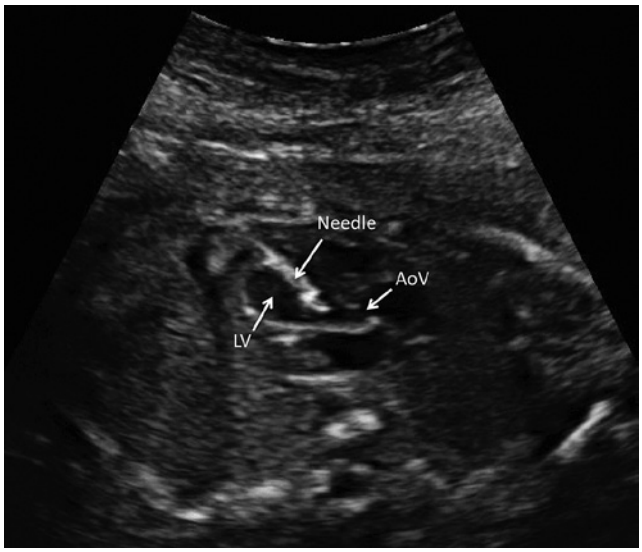


Figure 19.3 Needle in the fetal left ventricle. The fetus is supine, and the mother's abdominal wall is at the top of the image. LV, left ventricle, AoV, aortic valve. (Source: Dr. A. Marshall. Reproduced with permission.)

ventricular access, fetal hemodynamic changes including bradycardia and ventricular dysfunction may occur before balloon insertion, during inflation, or even after the instruments have been removed [212]. Fetal resuscitation drugs must be immediately available. Intracardiac, or less commonly, intramuscular administration of epinephrine and/or atropine are used for sustained fetal bradycardia. Hemopericardium is another common problem during FCIs. Hemodynamically significant hemopericardium should be drained promptly as the effusion has the tendency to coagulate within a few minutes [203]. Fetal demise rates of 4 to 17% have been reported following FCI [205, 213, 214]. Most recent data suggests that FCI has a low risk of maternal complication and a negligible impact on the further course of pregnancy and delivery [205, 213, 214].

Fetal aortic valvuloplasty for aortic stenosis with evolving HLHS is the most commonly performed FCI. Successful valvuloplasty leads to improvement in left heart hemodynamics, specifically antegrade aortic arch flow and bidirectional patent foramen ovale flow, in ~50% of fetuses [202]. In the Boston Children's Hospital cohort, improved technical success rate and modified selection criteria have led to an increased likelihood of biventricular circulation. In the recent era, 59% of liveborn patients that underwent fetal aortic valvuloplasty had a biventricular outcome [214]. Among those who achieved biventricular circulation, the vast majority required further surgical and/or catheter-based interventions after birth, including interventions on the aortic valve, mitral valve and aortic arch, and endocardial fibroelastosis resection. Medium- and long-term survival and LV function data are not yet available.

Fetuses with membranous pulmonary atresia, intact ventricular septum, and evolving hypoplastic right heart can also be candidates for FCI. The *z*-score (number of standard deviations below normal for gestational age) of the fetal tricuspid annulus and qualitative assessment of RV size are used to predict the potential growth of the RV and therefore chances for a biventricular circulation [215, 216]. Fetuses with technically successful fetal pulmonary valvuloplasty have stable z-scores of right heart structures, in contrast to fetuses with unsuccessful fetal pulmonary valvuloplasty who experience progressive RV and tricuspid valve hypoplasia [202]. In the largest published experience from the International Fetal Cardiac Registry, 31% of 16 fetuses with pulmonary atresia or severe pulmonary stenosis had postnatal biventricular circulation after fetal pulmonary valvuloplasty [213].

For fetuses with HLHS and intact or restrictive atrial septum, FCI has been used to prevent severe neonatal hypoxia and death, and to reduce the lung disease that accompanies chronic *in utero* pulmonary venous hypertension [202]. FCI on the atrial septum is typically performed at 24–30 weeks' gestation in selected fetuses, selected based on abnormal pulmonary vein Doppler profile, a sensitive and specific predictor of severe neonatal distress. The atrial septum is commonly thickened, and most centers attempt to maintain patency of the atrial communication by placing an atrial septal stent. No survival benefit to date has been demonstrated from fetal FCI on the atrial septum [217]. Many of the atrial communications become smaller in late gestation and significant lung disease has already developed in most of these fetuses by midgestation [202].

In summary, FCIs are technically feasible and can improve short-term outcomes in selected patient groups but are associated with a significant risk of fetal demise (~10%) and the potential for maternal harm. Long-term benefits are still to be determined, and the discussion regarding biventricular repair at all costs vs. univentricular palliation is ongoing. Further advances in imaging and equipment technology will allow better patient selection and earlier, possibly even more complex, interventions. Multi-center efforts to collect short- and long-term outcome data will be important to assess the effectiveness and safety of FCIs.

KEY POINTS: FETAL CARDIAC INTERVENTIONS AND SURGERY

- Fetal cardiac interventions can be classified into pharmacological, open, and catheter-based interventions.
- The rationale for FCI is the prevention of fetal demise or early neonatal death and/or ventricular hypoplasia in cases of critical aortic stenosis or pulmonary atresia by restoration of more normal blood flow patterns.
- Currently, percutaneous closed interventions, using 18- or 19-gauge access cannulas, guidewires, and balloon catheters, are mainly used to treat selective patient groups with documented short-term benefits:
  - Fetal aortic stenosis with evolving HLHS
  - Fetal PA/IVS with evolving right heart hypoplasia
  - Fetal HLHS with intact or highly restrictive atrial septum.
- Catheter-based FCI is associated with a 45% risk of significant intraoperative hemodynamic instability requiring fetal resuscitation and a ~10% risk of fetal demise.

Delivery room emergencies in complex congenital heart disease

Because of the increasing frequency of accurate prenatal diagnosis of CHD, and improved outcomes when infants with complex CHD are born in a cardiac surgical center, a multidisciplinary approach to emergent post-delivery resuscitation and operative or catheter treatment is crucially important in the highest risk patients [218, 219]. Although the cardiovascular anesthesiologist is not usually present in the delivery room, they must be involved in collaborative planning for the delivery, and preparations for emergent catheter, operative, or bedside intervention. The logistics of resuscitation in the delivery room, vs. transport to the site of interventional care should be planned as far in advance as possible. Tables 19.4 and 19.5 present CHD lesions and strategies for immediate postdelivery resuscitation and treatment [220]. Not surprisingly, several of the highest risk lesions post-delivery are also candidates for fetal therapy (see above). These include HLHS with an intact or restrictive atrial septum, obstructed TAPVR, severe Ebstein anomaly, and congenital complete heart block. Delivery in a cardiac center as close to the site of intervention as possible, i.e., catheterization laboratory or cardiac operating room, is essential. In some cases, direct transfer is indicated; cesarean delivery in an adjacent OR for the highest risk patients has been described. The *ex-utero* intrapartum therapy (EXIT) procedure has been reported in the management of HLHS with an intact atrial septum, either as sole support while surgical atrial septectomy is performed before full delivery of the infant, or as a bridge to the institution of CPB for the atrial septectomy [221, 222].

Table 19.4 Emergent neonatal cardiac intervention (ENCI) classification system

ENCI risk	Level	Emergent neonatal cardiac intervention	PGE dependent	Mode of delivery an issue	NICU acuity level	Neonatologist present in DR	Critical care transport needed	Cardiology, CT surgery, CTICU, OR/Cath lab on standby	Examples of CHD
I	Low risk	No	No	No	Low	No	No	No	ASD, VSD, mild PS
II	Intermediate risk	No	No	No	Mid	Possibly	Possibly	No	CAVC, TOF/PS, Truncus Arteriosus
III	Moderate risk	Possibly	Likely	Possibly	High	Yes	Yes	Possibly	HLHS, TOF/PA, PA/IVS
IV	High risk	Likely	Likely	Yes	High	Yes	Yes	Yes	D-TGA/RAS, HLHS/RAS, obstructed TAPVR

ASD, Atrial Septal Defect; CAVC, complete atrioventricular canal defect; Cath, catheterization; CT, Cardiothoracic; CTICU, Cardiac Intensive Care Unit; DR, Delivery Room; D-TGA, D-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; NICU, Neonatal Intensive Care Unit; OR, Operating room; PA/IVS, pulmonary atresia with intact ventricular septum; PGE, Prostaglandin E1; PS, pulmonary stenosis; RAS. restrictive atrial septum; TAPVR, Total Anomalous Pulmonary Venous Return; TOF, tetralogy of Fallot; VSD, Ventricular Septal Defect.

Table 19.5 Delivery room management recommendations for ENCI level 4 cardiac lesions

Cardiac lesion	DR preparation	DR resuscitation
D-TGA with restrictive/intact atrial septum	PGE availableIV and UV catheter setupInhaled nitric oxide if ductal flow abnormalNotify cardiology, cath lab	Initiate PGE via umbilical or peripheral lineIntubation, mechanical ventilation (SPO_2 goal 75–85%)Consider inhaled nitric oxide if ductal flow abnormalImmediate transfer to cath lab for balloon atrial septostomy
HLHS with restrictive/intact atrial septum	PGE availableIV and UV catheter setupNotify cardiology, cath lab and/or CT surgery	Initiate PGE via umbilical or peripheral lineIntubation, mechanical ventilation (SPO_2 goal 75–85%)Immediate transfer to cath lab or OR for intervention to open atrial septum
Severe Ebstein anomaly	PGE availableIV and UV catheter setupAntiarrhythmics if concern for tachyarrhythmia	Initiate PGE via umbilical or peripheral lineIntubation, mechanical ventilation (SPO_2 goal > 90%)Consider 100% FiO_2 and inhaled nitric oxide to lower PVRTransfer to ICU when stabilized
TOF/APV	IV and UV catheter setupNotify cardiology	Consider 100% FiO_2Prone positioning, try to avoid intubation if possible (risk of air trapping)Intubation and mechanical ventilation if necessary, consider higher PEEP (SPO_2 goal > 90%)Transfer to ICU when stabilized

(*Continued*)

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Table 19.5 (Continued)

Cardiac lesion	DR preparation	DR resuscitation
Obstructed TAPVR	PGE availableIV and UV catheter setupNotify cardiology, CT surgery	Initiate PGE via umbilical or peripheral lineIntubation, mechanical ventilation (SPO_2 goal 75–85%)Consider ECMOImmediate transfer to OR for surgical repair
Tachyarrhythmias	Cardiac Monitor available for rhythm analysisIV and UV catheter setupAdenosine and antiarrhythmics availableDefibrillator and neonatal pads availableNotify cardiology	Cardioversion if unstableRapid administration of adenosine via umbilical or peripheral line, if concern for SVTTransfer to cardiac center with electrophysiology when stable ECG, initiation of antiarrhythmic
CHB with HR <55 bpm	Cardiac Monitor available for rhythm analysisIV and UV catheter setupIsoproterenol and/or epinephrinePacer/defibrillator available (set to pacing mode)Temporary pacing padsNotify cardiology, CT surgery	Initiate chronotropic agent via umbilical or peripheral line, if HR <55 bpmTranscutaneous pacing, if HR <55 bpmIntubation, mechanical ventilation, if hydrops or myocardial dysfunction (SPO_2 goal > 90%)Immediate transfer to ICU, possibly to OR for temporary vs permanent pacing wires

CHB = complete heart block; CT = cardiothoracic; DR = delivery room; D-TGA = transposition of the great arteries; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; HLHS = hypoplastic left heart syndrome; HR = heart rate; ICU = intensive care unit; OR = operating room; PGE = prostaglandin E1; PVR = pulmonary vascular resistance; SPO_2 = arterial oxygen saturation; TAPVR = total anomalous pulmonary venous return; TOF/APV = tetralogy of Fallot absent pulmonary valve.

Selected references

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart

3 Glatz AC, Petit CJ, Goldstein BH, et al. Comparison between patent ductus arteriosus stent and modified Blalock-Taussig shunt as palliation for infants with ductal-dependent pulmonary blood flow: insights from the congenital catheterization research collaborative. Circulation 2018;137:589–601. Multicenter comparison of palliative PDA stent and BT shunt for infants with ductal-dependent pulmonary blood flow supporting PDA stent as a reasonable alternative to BT shunt in select patients.

12 Wypij D, Newburger JW, Rappaport LA, et al. The effect of duration f deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1397–403. Landmark paper in which the authors found a non-linear relation between the duration of DHCA and worsening neurodevelopmental outcomes. An absolute "safe" duration could not be established.

17 Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;1(8527):243–8. Classic study demonstrating that preterm babies undergoing ligation of PDAs can mount significant stress responses with negative impact on the postoperative course. Anesthesia with 10 μg/kg fentanyl may diminish this response and improve postoperative outcomes.

19 Baum VC, Palmisano BW. The immature heart and anesthesia. Anesthesiology 1997;87:1529–48. Comprehensive review article describing the functional, metabolic, and cytoarchitectural characteristics of the immature heart.

98 Algra SO, Jansen NJG, van der Tweel I, et al. Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques. Circulation 2014;129:224–33. Randomized, controlled trial comparing DHCA and antegrade cerebral perfusion during aortic arch reconstruction in 37 neonates. New cerebral injury was evident on MRI at 1 week in three-quarters of patients, irrespective of perfusion technique. There was no difference in motor or cognitive outcomes at 24 months.

109 Hickey EJ, Nosikova Y, Zhang H, et al. Very low-birth-weight infants with congenital cardiac lesions: is there merit in delaying intervention to permit growth and maturation? J Thorac Cardiovasc Surg 2012;143:126–36. Single center study of 1618 neonates admitted for a congential heart defect demonstrating the relationship between birthweight and survival, with an inflection point at 2.0 kg. Imposed delays to surgery for growth and maturation were found to neither compromise nor improve survival.

112 Voynow JA. "New" bronchopulmonary dysplasia and chronic lung disease. Paediatr Respir Rev 2017;24:17–8. Concise review of BPD and chronic lung disease in the era of antenatal glucocorticoids, postnatal surfactant and noninvasive ventilatory support.

158 Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. Arch Dis Child Fetal Neonatal Ed 2008;93:F153–61. Comprehensive review of the pathogenesis of periventricular leukomalacia in the premature infant and discussion of potential preventive interventions.

202 Friedman KG, Tworetzky W. Fetal cardiac interventions: Where do we stand? Arch Cardiovasc Dis 2020;113:121–8. Comprehensive review of indications, technique and procedural outcomes of catheter-based FCIs.

209 Brusseau R, Mizrahi-Arnaud A. Fetal anesthesia and pain management for intrauterine therapy. Clin Perinatol 2013;40:429–42. General review of anesthesia for fetal interventions describing key aspects of the fetal physiology, anesthetic options, routes for fetal drug delivery, monitoring, and methods of intrauterine fetal resuscitation.

CHAPTER 20

Anesthesia for Adults with Congenital Heart Disease

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Introduction

The adult congenital heart disease (ACHD) population is in constant growth due to improvements in diagnosis and treatment. In the last 70 years, the survival rate improved five times from 15% in the early 50s to more than 90% in the current era [1, 2]. In a comprehensive prevalence study in the province of Quebec, the median age of all individuals with severe congenital heart disease (CHD) in 1985 was 11 years and increased to 17 years in 2000. At that time, the ACHD population exceeded for the first time the children living with severe CHD. Currently, the ratio continues to rise in favor of the adult populations [3]. Worldwide the estimated prevalence of CHD population has also increased by 18% from 1990 to 2017 [4]. This increase is mostly due to increased survival rate in middle to higher income countries since the prevalence rates of CHD at birth has changed modestly.

The are several challenges facing the anesthesiologist taking care of patients with ACHD. First, the ACHD population requires anesthesia often to treat residual cardiac defects, arrhythmias, and heart failure since most of these patients have sequelae from their initial repair or palliation or the natural progression of the CHD. Second, access to medical information and previous surgical intervention is challenging since the transition of care from pediatric to adult service is not seamless [5, 6]. Finally, ACHD patients with moderate-to-severe disease by anatomic and or physiological criteria have an increased perioperative risk in cardiac and in non-cardiac surgery [7, 8]. Risk stratification is key to optimize high risks patients perioperatively and define the best setting for treatment and recovery [9].

The perioperative risk of patients with ACHD is related to the anatomical complexity of CHD, physiologic status and acquired comorbidities. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline for the Management of ACHD adds the patient's present physiological condition to the classic anatomical classification of CHD [10]. Traditional severe anatomical conditions include cyanotic CHD (unrepaired or palliated), double-outlet ventricle, interrupted aortic arch, mitral atresia, single ventricle, pulmonary atresia, transposition of the great arteries (TGA), and truncus arteriosus. From the physiological standpoint, higher

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risk patients include those in symptomatic heart failure (New York Heart Association Functional Class III–IV), severe aortic enlargement (diameter ≥ 5.0 cm), arrhythmias refractory to treatment, severe hypoxemia (saturation at rest <85%), and severe pulmonary hypertension (systemic or supra-systemic, Eisenmenger syndrome) and/or refractory end-organ dysfunction. Certainly, acquired comorbidities affect patients with ACHD more commonly than the general population. These include metabolic syndrome (central obesity, dyslipidemia, hypertension, and diabetes mellitus), renal dysfunction, liver failure, restrictive lung disease, developmental delays, and acquired neurological injury [11–15]. Despite a higher incidence of metabolic syndrome coronary artery disease prevalence is similar to the overall population. Restrictive lung disease is not only related to CHD but also to the number of thoracotomies [16].

There is no well-defined pathway to treat patients with ACHD. The treatment options are two, adult hospitals or children's hospitals without a clear best choice. Adult hospitals carry the expertise of treating adult patients with acquired disease but lack the CHD knowledge. Alternatively, children's hospitals have the skills to treat CHD, but they do not have the experience to treat adult-acquired disease [17]. Independently of the type of facility successful ACHD centers use a team approach with a wide variety of providers including pediatric, and ACHD cardiologists, surgeons, and pediatric cardiovascular anesthesiologists. Currently, in the United States, there are only 41 Adult Congenital Heart Association (ACHA) accredited programs in a total of 25 states to treat over a million patients. ACHA accredited programs have better outcomes than those without that expertise. ACHD programs need to develop a transitional program to decrease the attrition to follow-up. A comprehensive survey of patients with ACHD in North America identified that 42% of patients (mean age 19 ± 9.1 years) had gaps in the care of more than 3 years. This survey excluded adults cognitively incapable of responding directly to the survey and probably underestimates the gaps in care. The most common reasons cited for gaps in care were "feeling well," "changing or losing insurance," and "financial problems" for severe cardiac lesions. Many patients with ACHD perceive themselves as normal individuals who have had a heart problem in the past that is "fixed," and fail to appreciate the need for follow-up [18].

The goals of this chapter are to analyze the noncardiac sequelae of CHD and review the ACHD pregnancy consideration and the more prevalent cardiac lesions. Finally, the chapter will address the ACHD heart failure management (e.g., ventricular assist device and transplantation) and the management of the patient with ACHD for cardiac and noncardiac surgery.

Noncardiac sequelae of CHD

Pulmonary sequelae

Pediatric patients who undergo cardiothoracic operations are at increased risk of developing scoliosis [19]. The described risk factors include female gender, developmental delay, and presence of genetic syndrome (e.g., Down's or DiGeorge's). Traditionally thoracotomy has been described as a risk factor for developing scoliosis but newer rib sparing surgical approaches had challenged this concept [20]. The mechanism of this predisposition is probably multifactorial including surgical injury, diaphragmatic palsy, chest remodeling due to cardiomegaly, and asymmetric growth post-thoracotomy or sternotomy. Consequently, restrictive lung function is prevalent in surgically repaired CHD patients, and up 50% of these patients have restrictive spirometry testing profiles [21]. Patients with ACHD have decreased exercise tolerance based on oxygen consumption (VO_2) index, diminished forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), and significant restriction compared with normal (Figure 20.1) [22]. A diminished pulmonary function may have consequences postoperatively either in the recovery room or intensive care unit (ICU), and the ability to wean from the ventilator and needs to be addressed in the preoperative visit [23]. Moderate-to-severe impairment of FVC is a predictor of mortality in ACHD [24]. Figure 20.2 shows a representative patient with severe pulmonary sequelae.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a major perioperative risk factor in ACHD and is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization [25, 26]. PAH associated with ACHD can be classified into four groups:

1. *Systemic-to-pulmonary shunt with increased pulmonary vascular resistance (PVR)*. These shunts may be unrestricted atrial septal defects (ASDs), ventricular septal defects (VSDs), patent ductus arteriosus (PDA), or surgically created shunts such as the Blalock–Taussig (BT), Waterston, and Potts' shunts. A long-standing left-to-right shunt with a pulmonary-to-systemic flow ratio (Qp:Qs) exceeding 2:1 creates shear stresses and changes in the endothelium, and subsequent hypertrophy of the smooth muscle potentially causing PH. These defects are amenable to closure if the PVR index is <4 WU.m^2. If the PVR is higher than 4 but <8 WU.m^2 fenestrated closure could be attempted if there is a good response to disease-targeting therapy (DTT).
2. *Eisenmenger syndrome*. Long-standing systemic to pulmonary shunts leads to systemic pulmonary pressures and shunt reversal to right-to-left, and cyanosis will ensue. Defect closure is contraindicated and supportive therapy with anticoagulation and DTT is indicated.
3. *Primary pulmonary hypertension attributed to CHD, and yet the CHD lesion is quite mild*. Minor defects, such as a small ASD, and not considered the cause of PH. The clinical course of this type of PAH is like idiopathic PAH. The management is like Eisenmenger syndrome refraining from closing the defects and starting DTT.
4. *Pulmonary hypertension due to left heart disease*. Causative lesions include a regurgitant or stenotic systemic atrioventricular (AV) valve, aortic insufficiency (AI), or a failing systemic ventricle.

The anesthetic management of PH and weaning from cardiopulmonary bypass must be tailored to avoid vasoconstrictive triggers, minimizing PVR by optimal oxygenation, alkaline pH, and the use of the pulmonary vasodilators (e.g., nitric oxide, NO). In ICU, DTT should be started before attempting to wean ventilatory support and iNO. The DTT includes three pathophysiological pathways: the endothelin

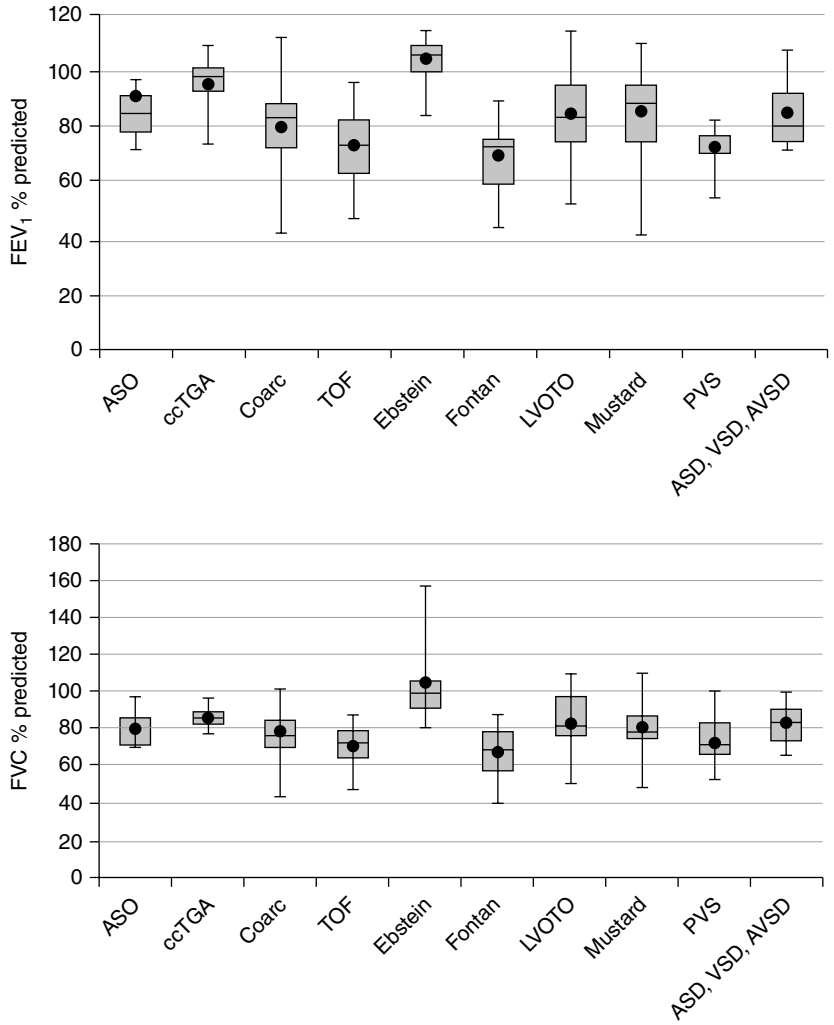


Figure 20.1 Spirometry profiles in adults with congenital heart disease. Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity. ASO, arterial switch operation; ccTGA, congenitally corrected transposition of the great arteries; Coarc, coarctation of the aorta; TOF, tetralogy of Fallot; LVOTO, left ventricular outflow tract obstruction; PVS, pulmonary valve stenosis; ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect. (Source: Ginde et al [22]. Reproduced with permission of John Wiley & Sons)

pathway (endothelin-1 receptor antagonists), NO pathway (phosphodiesterase type-5 inhibitors), and prostacyclin pathway (prostanoids). Bosentan an endothelin-1 receptor antagonist has shown long-term symptomatic benefits in exercise capacity in ACHD patients with PH [27]. Phosphodiesterase type 5 inhibitors besides the vasodilatory effect in pulmonary vasculature have a beneficial effect at a microcirculatory level in patients with ACHD [28]. Iloprost, a prostanoid, produces pulmonary vasodilation through the prostacyclin pathway, improves right ventricular function and exercise capacity in Eisenmenger patients [29].

Eisenmenger syndrome is a challenge, as the anesthesiologist must deal with both PH and the potential to exacerbate the right-to-left shunt, resulting in worsening cyanosis. It is more likely to present in patients with large and complex septal defects. The median survival after diagnosis of Eisenmenger syndrome is reported to be 35–60 years [30]. Patients with Eisenmenger syndrome will present for heart-lung transplantation, but outside of this context, interaction with an anesthesiologist will be limited to diagnostic investigations and noncardiac surgery. Generally, Eisenmenger patients are easier to manage than patients with primary PH, as the right ventricle (RV) is robust and accustomed to a high afterload. Bennet et al. showed that hypotension is common during induction of Eisenmenger's patients regardless of the agent used. The use of preemptive use vasopressor is recommended [31–33]. Manes et al. presented the survival data of ACHD patient with PH. The patients with small or corrected defects have the worse outcomes [34]. Chapter 33 contains an extensive discussion of PAH.

Hematological sequelae

Patients with cyanotic heart disease have erythrocytosis, an increase in the red cell line in response to hypoxia. Relative to the red cells there is a deficiency in vitamin K-dependent clotting factors, fibrinogen, and platelets [35]. Particularly single ventricles or cyanotic patients have an increased risk of thrombosis yet are frequently coagulopathic intraoperatively [36, 37]. Phlebotomy is inappropriate unless there are extreme symptoms of hyperviscosity, as iron

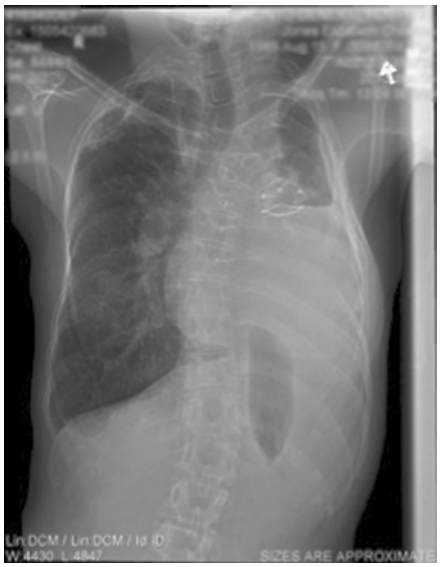


Figure 20.2 26-year-old with pulmonary atresia and right ventricle (RV) to pulmonary artery (PA) conduit. The patient's weight is 45 kg, and the previous history includes pneumonectomy at age 16 years, paralyzed vocal cord, asthma, bronchiectasis, kyphoscoliosis. Forced expiratory volume in 1 second (FEV1) is 600 mL (20% of normal). The patient has RV–PA conduit obstruction with an RV pressure of 48/25 mmHg, and elevated pulmonary vascular resistance at 8–10 Wood units.

deficiency with microcytosis is an independent risk factor for stroke, thrombosis, and hemoptysis [38].

Renal sequelae

Impaired renal function, as in patients with acquired heart disease, is a significant predictor of morbidity and length of stay in ACHD surgery [39]. Kwiatkowski et al. in a retrospective study described the principal risk factors for developing acute kidney injury after ACHD surgery [40]. Older age (≥35 years), preoperative left ventricular (LV) dysfunction, preoperative arrhythmia, longer bypass time, and vancomycin use were significant risk factors. The Acute Dialysis Quality Initiative Group has defined the range of renal dysfunction using the so-called "RIFLE classification system" (Box 20.1), which has been endorsed by the Multi-societal Database Committee for Pediatric and Congenital Heart Disease and further subdivided into renal insufficiency and renal dysfunction [41]. A total of 1,102 adult patients attending the Royal Brompton Hospital in London over a period between 1999 and 2006 had a serum creatinine measured and a glomerular filtration rate calculated. Renal dysfunction was mild in 41% of patients and moderate or severe in 9%. Not surprisingly, severe renal impairment correlated with increased mortality over the 4-year follow-up period [42].

Box 20.1: The RIFLE classification system

- Risk (R)—1.5-fold increase in serum creatinine, >25% decrease in glomerular filtration rate, or urine output <0.5 mL/kg/hour for 6 hours
- Injury (I)—two-fold increase in serum creatinine, >50% decrease in glomerular filtration rate, or urine output <0.5 mL/kg/hour for 12 hours
- Failure (F)—three-fold increase in serum creatinine, serum creatinine >4 mg/dL, >75% decrease in glomerular filtration rate, urine output <0.3 mL/kg/hour for 24 hours, or anuria for 12 hours
- Loss (L)—persistent acute renal failure defined as the need for renal replacement therapy for >4 weeks
- End-stage renal disease (E)—need for renal replacement therapy for >4 weeks.Source: Welke et al. [43]. Reproduced with permission of Cambridge University Press.

Neurological sequelae

Surgical, perfusion and interventional strategies allow early intervention in the neonatal period, with improved survival but with a concerning incidence of neurodevelopmental complications in survivors [44]. In CHD the lifetime impact of cardiovascular disease on neurovascular disease changes. In early childhood, neurodevelopmental disorders are the central issue but with age epilepsy, stroke and dementia become more prevalent [45]. Interestingly, the increased risk of epilepsy is also seen in nonsurgical CHD patients indicating the presence other neurodevelopmental factors unrelated with the perioperative period [46].

Patients with ACHD have an elevated risk of ischemic and hemorrhagic stroke [47]. Lanz et al. in a retrospective, population-based cohort study showed that almost 8% of patients with ACHD will experience a stroke in adulthood [48]. The risk of stroke was to 9–12 times higher in younger patients (<55 years old) up and only double older patients (55–64 years old). Severe ACHD and left-sided lesions carry the highest risk of stroke. The greatest predictors of ischemic stroke in patients with ACHD are heart failure, diabetes mellitus, and recent myocardial infarction. The thirty-day mortality after stroke is comparable to the general population.

Early-onset dementia is more prevalent in patients with ACHD, and the burden of this disease is likely to increase with the growing population [49]. Patients with ACHD carry several risk factors for dementia including genetic disorders (e.g., Down syndrome), stroke, heart failure, atrial fibrillation, and diabetes mellitus. ACHD centers must acknowledge and accommodate some aspects of the pediatric anesthesia practice. Inhalational inductions are less practical, and premedication with hypnotics, and occasionally intramuscular ketamine, may be necessary. Patients' impressions made on the first anesthetic encounter at the adult facility will influence future attitudes toward anesthetic care, and compliance with future visits.

Hepatic sequelae

ACHD is associated with liver dysfunction. The mechanism of liver failure is multifactorial secondary to CHD, surgical repair or palliation, or blood transfusion [50]. Liver dysfunction is caused by passive venous congestion (e.g., central venous hypertension) or low-output cardiac syndrome (LCOS). Tricuspid insufficiency and right ventricular failure cause liver failure by passive venous congestion. ACHD linked with passive venous congestion are repaired tetralogy of Fallot (TOF) with pulmonary insufficiency, Ebstein's anomaly, single ventricle physiology (e.g., Fontan and Glenn), TGA with atrial switch repairs (e.g., Mustard-Senning). Elevation of indirect bilirubin and prolonged international normalized ratio (INR) without affecting of the aminotransferases is typical in central venous hypertension. CHD conditions that cause LCOS, such as aortic coarctation or LV outflow tract obstruction, cause hepatic ischemia and eventually fibrosis. The ischemic burden is worse in the presence of an increased hepatic sinusoidal pressure.

Acute ischemic hepatitis caused by LCOS is characterized by marked early rises of transaminases, followed by later increases in bilirubin and prothrombin time.

Fontan patients are the highest ACHD risk group to develop liver failure with an incidence of over 40%, 30 years after the initial procedure [51]. Failing Fontan physiology patients are prone to develop liver fibrosis earlier due to the continuous back pressure on the sinusoids secondary to elevated non-pulsatile central venous pressure (CVP). There is a strong correlation between hepatic fibrosis and high hepatic venous pressures, low cardiac index, and ventricular function. The gold standard for diagnosis of Fontan associated liver disease is the percutaneous liver biopsy under ultrasound guidance. Transvenous biopsies can be obtained at the time of the cardiac catheterization and transhepatic gradient can be measured. An elevated hepatic venous pressure gradient >5 mmHg is indicative of parenchymal liver disease. Gradients over 10 mmHg are associated with portal hypertension complications (e.g., ascites and variceal hemorrhage) [52, 53].

Model for End-stage Liver Disease (MELD-XI) scores, excluding INR scores, is used to classify the severity of liver disease in ACHD. The advantage of the MELD-XI score is that the INR is excluded, and many patients with Fontan circulation are taking warfarin. In addition, there is a statistically significant correlation between MELD-XI values and hepatic total fibrosis scores [52]. Once a Fontan patient is diagnosed with cirrhosis, close surveillance for hepatocellular carcinoma and esophageal varices assessment is recommended.

There is no specific treatment for Fontan-associated liver disease. Medical treatment should optimize Fontan physiology by increasing cardiac output (e.g., afterload reduction) and decreasing CVP (e.g., diuretics). Additional etiologies of liver injury should be avoided with immunization (e.g., hepatitis A and B) and limiting other toxins (e.g., alcohol or obesity). Combined heart and liver transplant is the ultimate treatment of failing Fontan physiology with associated liver disease. Hofer et al. recently reviewed the anesthetic management of combined heart–liver transplantation in patients with Fontan-associated liver disease. The authors recommend keeping the transpulmonary pressure gradient close to 5 mmHg by optimizing preload, reducing PVR, and preserving single ventricular function [54]. Chapter 30 contains additional discussion of heart-liver transplantation.

KEY POINTS: NONCARDIAC SEQUELAE OF CHD

- Patients with ACHD can experience a wide range of noncardiac sequelae:
  - Pulmonary—restrictive lung disease and PAH
  - Hematological—erythrocytosis, polycythemia, and coagulopathy
  - Renal dysfunction—mild in 41%, moderate or severe in 9%
  - Neurological sequelae—developmental delay, cerebral abscess, stroke, and early dementia
  - Hepatic sequelae—hepatic congestion, dysfunction, and cirrhosis from right heart failure or elevated cavopulmonary pressures.

Vascular access considerations

Patients with ACHD undergo multiple interventions during infancy and childhood so by the time the reach adulthood the central and peripheral vascular access may be compromised. The use of ultrasound for vascular access is recommended in potential difficult intravenous access patients such as the ACHD population [55]. Chue et al. describe a 3.6% incidence of complications after femoral cannulation for percutaneous interventions in patients with ACHD [56]. The complications included hematoma and pseudoaneurysm.

The preoperative visit should include examining the extremities for cut-down scars and measuring blood pressure in all extremities. Planning for major cardiac surgery should consist of venous Doppler or magnetic resonance imaging (MRI) of the femoral vessels, central veins and arterial and venous studies. Computed tomography or MRI of the chest is essential to delineate the intrathoracic anatomy and the relationship between the heart and great vessels to the sternum [57]. The anesthesiologist should discuss plans for emergent cannulation of the femoral vessels in the event of a cardiac injury at sternotomy. Cardiac or vascular injury upon resternotomy in ACHD is more common in patients with extracardiac conduits and dilated structures (e.g., aorta, RV, or right atrium) [58]. One of the approaches to high-risk sternotomy patients is establishing cardiopulmonary bypass through peripheral cannulation before sternotomy [59].

Unrestricted shunts

There are two types of unrestricted shunts. First, simple shunts, such as ASDs, VSDs, large PDAs, and aortopulmonary collaterals have a left-to-right shunt in the presence of normal or low PVR, and pulmonary blood flow may exceed systemic blood flow. Second, complex congenital lesions palliated with systemic-to-pulmonary artery shunt (e.g., BT, Waterston–Cooley, or Potts' shunt) to augment pulmonary blood flow who may develop unilateral PAH. The Australian National registry for PAH in ACHD found that, of the first 50 registrants, 47 had systemic-to-pulmonary artery shunts [60]. At rest, breathing room air, these patients may have a 2:1 or as much as a 3:1 shunt ratio of pulmonary to systemic blood flow. The anesthesiologist should avoid 100% oxygen ventilation since it will lower the patient's PVR, converting a 2:1 shunt to a 4–5:1 shunt, causing metabolic acidosis from diminished systemic oxygen delivery. Unrestricted left-to-right shunts can reverse with a profound decrease in systemic vascular resistance (SVR). The coronary circulation is dependent on the diastolic pressure and will compete with the run-off into the pulmonary circulation when the PVR decreases by hyperventilation and 100% oxygen. After induction, baseline conditions should be targeted, maintaining the patient on a FiO_2 that recreates their room air oxygen saturations at rest to avoid increasing the shunt fraction and coronary ischemia. Ventilation should be at lung volumes close to functional residual capacity (FRC) and maintain a normal $PaCO_2$.

Pregnancy

The increase in adults living with CHD also reflected in the obstetrical population, with increasing numbers of women with ACHD needing pregnancy care. For example, in one

analysis, the number of women with ACHD presenting for delivery increased from 6.4 to 9.0 per 10,000 delivery hospitalizations [61]. Effective communication among the care team is essential, and anesthesiologists play a crucial role in assuring appropriate care for women with ACHD during pregnancy, labor, and delivery. Anesthesiologists must understand the effect of pregnancy on the cardiovascular system, the unique physiology of each patient's cardiac lesion or surgical repair, and the cardiovascular impact of various anesthetic techniques used on labor and delivery.

Relevant physiologic changes during pregnancy

A growing fetus requires increased oxygen delivery to the uteroplacental unit. Cardiac output increases by approximately 50% during pregnancy by increasing heart rate and stroke volume to keep up with the demand. Plasma volume significantly increases during pregnancy, reaching its peak around the early third trimester. Sympathetic tone increases in the first trimester (Figure 20.3) [62]. Transthoracic echocardiography (TTE) demonstrates increased cardiac performance and progressive LV remodeling. LV mass and LV end-diastolic diameter increase, while LV strain decreases. These values return to normal in the postpartum period [63]. Systemic and PVRs both decrease. Mean arterial blood pressure decreases before returning to near-normal values at the end of the third trimester [64]. Central filling pressures typically remain normal. Pregnancy is also associated with dilutional anemia. It is a hypercoagulable state with increases of most coagulation factors, a decrease in Protein S activity, and acquired Protein C resistance [65].

Labor and delivery bring additional cardiovascular demands that place stress on the heart. Autotransfusion from uterine contractions increases plasma volume and cardiac output up to 50% more than the pregnancy baseline throughout labor. In addition, painful contractions increase heart rate and SVR. During delivery, there is a large autotransfusion from uterine involution. This autotransfusion increases the circulating volume up to 100% over the baseline pregnant state, potentially overwhelming an already fragile circulation. As a result, it is a typical time for heart failure to occur [66, 67].

Cardiac risk assessment before and during pregnancy

Cardiac and fetal risk during pregnancy and the postpartum period depends on the nature of the patient's cardiac lesion, pre-pregnancy functional status, and general health. Simple lesions, such as a repaired ASD or mild pulmonic stenosis, do not carry a significantly increased risk over the general population. However, complex ACHD, such as a Fontan circulation or unrepaired cyanotic heart disease, poses a greater risk to the patient and may become life threatening [68].

Ideally, patients with ACHD should plan their pregnancy after consultation at a tertiary care center with a cardio-obstetric team. The team should consist of a high-risk obstetrician, cardiologist, and obstetric anesthesiologist, all of whom have experience caring for patients with ACHD. Other experts should be consulted as necessary and include a cardiac anesthesiologist, cardiothoracic surgeon, cardiovascular intensivist, geneticist, neonatologist, hematologist, and others. In addition, preconception counseling should give the woman a clear understanding of the risks of pregnancy for her and her child. In some cases, additional testing and procedures may be warranted before it is deemed safe to embark upon pregnancy. Exercise testing is a valuable tool to aid in maternal and fetal risk stratification. Lack of a chronotropic response to exercise is predictive of both maternal and neonatal events [69]. Once pregnancy is confirmed, high-risk patients should be referred to a tertiary care program with expertise in pregnancy in ACHD.

Estimation of maternal and fetal risk during pregnancy and the postpartum period considers the mother's underlying cardiac condition and the presence or absence of risk

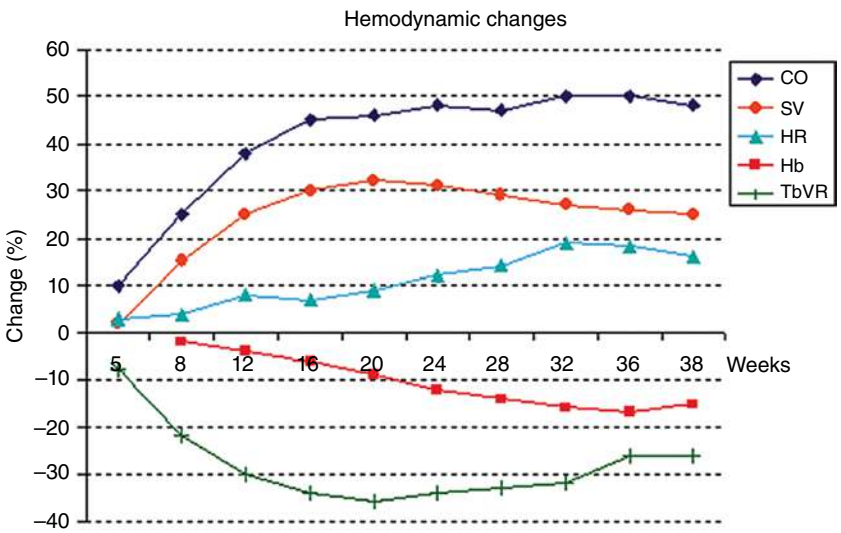


Figure 20.3 Hemodynamic changes in pregnancy. CO, cardiac output; SV, stroke volume; HR, heart rate; Hb, hemoglobin; TPVR, total peripheral vascular resistance. (Source: Ruys et al [62]. Reproduced with permission of Elsevier).

factors. The modified WHO (mWHO) pregnancy classification is regarded as the most accurate risk classification [64]. However, multiple risk scores are based on studies that have examined maternal and fetal risk in patients with cardiac disease. The mWHO classification is presented in Table 20.1 [68]. Its assessment of risk is based purely on underlying cardiac condition, assuming the mother is otherwise optimized.

In 2001, a large prospective observational trial examined 599 pregnancies in women with CHD (74%), acquired heart disease (22%) and arrhythmia (4%). A primary cardiac event occurred in 80 pregnancies (13%). Everyday cardiac events included heart failure and arrhythmia. They proposed four predictors of maternal cardiac complication (the CARPREG I score): prior cardiac event or arrhythmia, NYHA class >II or cyanosis, left heart obstruction, and systemic ventricular dysfunction [70]. An updated risk index, CARPREG II, was published in 2018. It included 1938 pregnancies in women with congenital (63.7%) and acquired (22.9%) heart disease. The new score incorporates different risk elements, including lesion-specific variables, patient-specific variables, and one process of care variable. It is outlined in Table 20.2 and Figure 20.4 [67]. The maternal complication rate was 16%, unchanged from their 2001 study. Arrhythmia (9.3%) and heart failure (6.2%) remained the most common cardiac events. Arrhythmias were most likely to occur in the antepartum period, where heart failure was most observed in the third trimester or the early postpartum period [67].

Table 20.2 CARPREG II risk stratification index

PREDICTOR	SCORE
Prior cardiac events or arrhythmias	3
Baseline NYHA III-IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High-risk left-sided valve disease/left ventricular outflow tract obstruction	2
Pulmonary hypertension	2
Coronary artery disease	2
High-risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

Source: Adapted from Silversides et al [67].

Table 20.1 Modified WHO classification of maternal cardiovascular risk

	mWHO I	mWHO II	mWHO II-III	mWHO III	mWHO IV
Diagnosis (if otherwise well and uncomplicated	Uncomplicated, small or mild • PS • PDA • MVP Successfully repaired simple lesions (ASD, VSD, PDA, APVR). Atrial or ventricular ectopic beats, isolated	Unoperated ASD or VSD Repaired TOF Most arrhythmias	Mild LV impairment HOCM Native or tissue valvular heart disease not considered WHO I or IV Marfan syndrome without aortic dilatation Aorta <45 mm in aortic disease associated with bicuspid aortic valve Repaired coarctation	Mechanical valve Systemic RV Fontan circulation Cyanotic heart disease (unrepaired) Other complex congenital heart disease Aortic dilatation 40–45 mm in Marfan syndrome Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve	PHTN of any cause Severe systemic ventricular dysfunction (LVEF <30%, NYHA III–IV) Previous peripartum cardiomyopathy with any residual impairment of left ventricular function Severe mitral stenosis, severe symptomatic aortic stenosis Marfan syndrome with aorta dilated >45 mm Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve Native severe coarctation
Risk	No detectable increased risk of maternal mortality and no/mild increase in morbidity.	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate-to-severe increase in morbidity	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium	Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III.
Maternal cardiac event rate	2.5–5%	5.7–10.5%	10–19%	19–27%	40–100%

Abbreviations: PS, pulmonary stenosis; PDA, patent ductus arteriosus; MVP, mitral valve prolapse, ASD, atrial septal defect; VSD, ventricular septal defect, APVR, anomalous pulmonary venous return; HOCM, hyperthrophic obstructive cardiomyopathy; RV, right ventricle
Source: Adapted from Canobbioet al [68].

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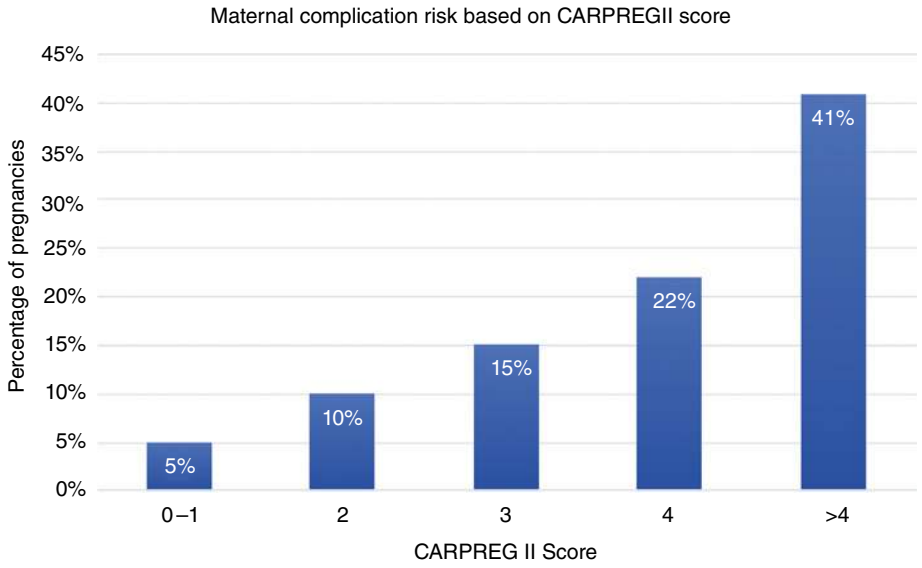


Figure 20.4 Maternal complication risk based on CARPREGII score. (Source: Silversides et al [67]. Reproduced with permission of Elsevier).

In a more extensive retrospective review from the ZAHARA group, 1802 pregnancies were observed in women with ACHD. The maternal cardiac complication rate was 7.6%. The most common maternal cardiac complications were arrhythmias (4.7%) and heart failure (1.6%). They confirmed several risk factors from the CARPREG studies. In addition, they identified further risk factors: the use of cardiac medication before pregnancy and systemic and pulmonic AV valve regurgitation in the context of complex ACHD [71]. A smaller study, examining 90 pregnancies in women with ACHD, identified two additional risk factors: impaired sub pulmonary ventricular systolic dysfunction and severe pulmonary regurgitation [72]. Single ventricle physiology was a risk factor for maternal cardiac events in a ACHD population [73].

External validation and comparison of the CARPREG I, ZAHARA, and mWHO risk classification systems in a ACHD population was undertaken in 2014. The mWHO score was best able to discriminate risk for cardiovascular events. In addition, a combination of the mWHO score, the total number of cardiovascular predictors, and disease complexity further improved prediction [74].

Maternal obstetric and fetal risks

The most common fetal complications in women with ACHD include premature birth (12–19%) and small for gestational age (SGA) birth weight. In addition, neonatal death occurred at a higher rate than the general population, ranging from 2.8–5%. There was also a higher observed incidence of intrauterine growth restriction (IUGR), neonatal intensive care (NICU) admission, and neonatal CHD [70–74]. The increase in premature births has two causes: preterm labor and iatrogenic premature delivery due to maternal health status or decompensation. Risk factors for fetal complications include maternal NYHA class >II, cyanosis, maternal anticoagulation, left heart obstruction, mechanical valve, cardiac medications during pregnancy, single ventricle physiology, severe pulmonary hypertension, smoking, and multiple gestations.

Patients with ACHD are at elevated risk for preeclampsia and postpartum hemorrhage (PPH). Risks for preeclampsia included nulliparity, systemic lupus erythematosus (SLE), and aortic coarctation [61]. In addition, several studies have identified CHD as an independent risk factor for PPH, and patients with Fontan circulation had a particularly elevated risk [75–77]. Peripartum anticoagulation and cyanosis are other identified risk factors for PPH [70].

Care during pregnancy

Anticoagulation

While anticoagulation during pregnancy is a risk factor for PPH and neonatal complications, for some conditions, the additional thrombotic risk conferred by pregnancy and the catastrophic effect of a thrombus in these conditions is significant. These conditions include a Fontan circulation or the presence of a mechanical valve [78–81]. The balance of risk and benefit for anticoagulation in pregnant patients with ACHD is an individualized decision.

Low-molecular-weight heparin (LMWH) is the preferred anticoagulant during pregnancy. Neither unfractionated heparin (UFH) nor LMWH crosses the placenta. LMWH is the anticoagulant of choice over UFH due to its reliability and relative ease of dosing. It is also associated with fewer injection site reactions and carries a lower risk of heparin-induced thrombocytopenia (HIT). However, the longer half-life LMWH and the inability to completely reverse its anticoagulant effect may limit the ability to provide neuraxial anesthesia. Warfarin is typically avoided during pregnancy as it is associated with well-known fetal malformations, particularly with exposure in the first trimester. Alternatives to warfarin should be used if clinically feasible. Direct oral anticoagulants have gained popularity for anticoagulation for several indications. However, there is scant data for use during pregnancy, and they are not recommended [82].

The presence of a mechanical valve is a known risk factor for cardiac complications [64, 67, 71]. The main risks are

valve thrombosis and bleeding complications related to anticoagulation. In a 2015 study, women with a mechanical valve only had a 58% chance of having an event-free pregnancy, 4.7% experienced valve thrombosis, which carried a 20% mortality rate. Hemorrhage occurred in 23% of patients, usually around the time of delivery [83]. Management of anticoagulation in this population is a challenge. Multiple studies have shown an increased risk of thrombosis in mechanical valve patients treated with LMWH vs. warfarin [83–86]. Warfarin is optimal for thrombosis prevention and is recommended for use during pregnancy in patients with a mechanical valve despite the risk of embryopathy. Patients may remain on warfarin during their entire pregnancy, or warfarin can be changed to LMWH or UFH for the first trimester and again after 36 weeks [64].

Cardiac procedures during pregnancy

Patients may present in pregnancy for cardiac interventional procedures or cardiac surgery. Ideally, cardiac procedures will occur in the second trimester when organogenesis is complete, and the risk of premature labor is still low. The uterus must be double shielded from radiation exposure during catheterization. Appropriate fetal monitoring is indicated both for intervention if the fetus is viable and to optimize hemodynamics in response to fetal distress. Discussion with the obstetric team should take place on the response to the diagnosis of fetal distress. The anesthesiologist should be cardiac trained with ACHD expertise. Cardiac surgery and perfusion should be on standby, and appropriate ICU resources available for the mother and fetus. Maternal cardiac surgery should only be performed during pregnancy if it is urgent, as in LV obstruction with symptoms at rest, or emergent, as in aortic dissection or a thrombosed mechanical systemic AV valve. Cardiac surgery during pregnancy and the use of cardiopulmonary bypass carries a high risk of fetal mortality. Normothermic perfusion, mean arterial pressure (MAP) >70 mmHg, minimal CPB times, and bypass pump flows >2.5 L/min/m^2 are optimal to minimize fetal risk. Hypocapnia, which ordinarily may be used for patient's dependent on a low PVR (TOF, Ebstein's anomaly, and Fontan circulation), has adverse effects causing uteroplacental vasoconstriction and fetal hypoxia and should therefore be avoided. If the fetus is viable, a caesarean section (C-section) may precede the urgent cardiac surgery [69, 87, 88].

Delivery planning

Multidisciplinary collaboration is essential to planning a safe delivery for mother and baby. Thoroughly assessing each patient's risk and anticipated complications allow mobilization of appropriate resources and determining who needs to be involved in the patient's delivery. Additional teams consulted may include ICU, cardiac surgery, cardiac anesthesia, and others. The team should also determine the optimal delivery mode, location, timing, and anesthetic plan.

The delivery hospital must have the necessary resources to care for the patient and handle any likely complications. This level of care depends on the estimate of the patient's risk and severity of her condition. For example, low-risk patients, mWHO class I and II, estimated cardiac event risk <10%, could safely be delivered at a local hospital. Patients with an intermediate risk (mWHO class II-III, calculated risk 10–19%) should deliver at a higher-level referral enter, while extraordinary risk patients (mWHO class II or IV) should refer to a tertiary care center experienced in the care of patients with ACHD [64, 89].

The mode of delivery determines birth location within the hospital, need for invasive monitoring, access to the escalation of care, and ability to perform emergency surgery quickly. The team should determine what resources and monitoring are necessary for delivery and then decide which location in their hospital best fulfill those needs. For example, if a C-section is planned, the operating room should be equipped to accommodate standard C-section needs in addition to possible contingencies, including demand for emergent ECMO cannulation or transesophageal echocardiography (TEE) and neonatal resuscitation.

Vaginal delivery is preferred in patients with ACHD unless an obstetric indication for C-section is present. Elective C-section based on maternal cardiac disease is not recommended, as it does not confer maternal benefit but may carry increased neonatal risk [90]. Vaginal delivery is associated with decreased blood loss and a lower risk of venous thromboembolism. For certain patients, an assisted vaginal delivery minimizes Valsalva and has beneficial hemodynamic effects. C-section recommendations include acute intractable heart failure, patients presenting in labor on oral anticoagulants, aggressive aortopathy, and severe pulmonary hypertension [64].

During labor, painful contractions can lead to tachycardia, hypertension, and hyperventilation. Early labor epidural placement can mitigate these unwanted effects. Sympathectomy associated with epidural local anesthetic administration causes vasodilation and can lead to hypotension. Therefore, cautious administration of a pre-load or co-load of IV fluid before or during epidural placement is beneficial. If the plan is to assist the second stage, good sacral nerve root coverage is required. The use of a combined spinal-epidural (CSE) or dural puncture epidural (DPE) technique achieves good sacral coverage. Opioid-only intrathecal injection (10 mcg Fentanyl) should be used in CSE to minimize the extent of sympathectomy and prevent hypotension. For patients with intracardiac shunts, consider using saline rather than air for the loss of resistance technique to minimize inadvertent air injection into a blood vessel during epidural placement. We do not advise the use of epinephrine in the epidural test dose. The intravascular injection of epinephrine could be detrimental to patients at high risk of arrhythmia. An alternative test dose is epidural fentanyl 50–100 mcg [91].

For patients undergoing C-section, neuraxial anesthesia is preferred over general anesthesia. In Figure 20.5, the advantages, and disadvantages of each are outlined. The selection of neuraxial technique depends on the physiology and severity of the patient's cardiac lesion. Spinal anesthesia produces a quick onset, reliable, dense surgical block. However, it is also accompanied by a rapid sympathectomy which causes an acute decrease in preload and afterload. Preload-dependent patients or severe (mWHO III-IV) lesions will not tolerate the sympathectomy. Epidural anesthesia can be titrated to ensure a slower onset and slow start

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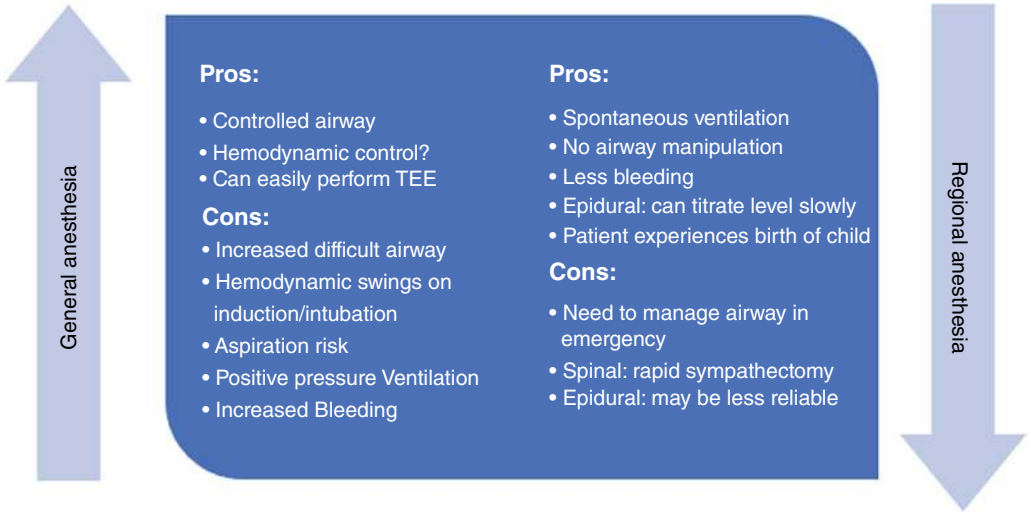


Figure 20.5 Advantages, and disadvantages of the administration of general vs. neuraxial anesthesia for cesarean section.

sympathectomy but may produce a less dense or unilateral block that is inadequate for surgical anesthesia. A CSE with intrathecal opioids or a sequential CSE, in which a small dose of local intrathecal anesthetic (2.5–5 mg 0.75% hyperbaric bupivacaine) is given and then supplemented with a local epidural anesthetic, can provide the balance between a reliable, dense block and the need for slow titration to avoid rapid sympathectomy, decreased SVR, and hypotension. Neuraxial anesthetic dosing recommendations for cesarean delivery are summarized in Table 20.3.

Anticoagulated patients require general anesthesia, and those unable to lay flat, critically ill requiring mechanical ventilation, or emergent delivery. Induction and maintenance of anesthesia should balance obstetric and cardiac considerations. In obstetric patients, increased aspiration risk leads to the use of rapid sequence induction. One should avoid opioids before delivery due to concern for neonatal sedation and respiratory depression. However, patients with high-risk cardiac lesions may require a slower induction to prioritize hemodynamic stability. Therefore, the administration of opioids to blunt the hypertensive response to laryngoscopy may be reasonable.

Adequate monitoring for the patient during delivery, whether vaginal or C-section, is vital for early recognition of maternal warning signs. For vaginal delivery, intermittent noninvasive blood pressure and pulse oximetry are essential for cardiac patients. Telemetry during and after delivery is mandatory for patients at risk for arrhythmia. For patients at higher risk of decompensation, invasive arterial blood pressure or CVP monitoring can be considered. Point of care TTE can be helpful to serially monitor cardiac function in patients with depressed systemic ventricular ejection fraction. For C-sections, standard monitors are sufficient for low and intermediate-risk patients. High-risk patients will likely require invasive arterial blood pressure or CVP monitoring and possibly pulmonary artery (PA) catheter placement. In patients who are under general anesthesia, TEE can be used.

Patients with ACHD need an individualized transfusion plan before delivery since they have an elevated risk of PPH. Most uterotonic medications have cardiovascular effects and need to be administered with caution. The hemodynamic results of commonly used uterotonic drugs are summarized in Table 20.4 [92]. Tranexamic acid (TXA) reduced PPH mortality in the WOMAN trial, which included over 20,000 women worldwide. There was no difference in cardiac failure, thromboembolism, or seizure between the TXA and placebo groups [93].

KEY POINTS: PREGNANCY IN ACHD

- Pregnancy in ACHD is associated with a 7–16% incidence of adverse cardiac events.
- Assess the cardiac pregnancy risk using the mWHO classification.
- High-risk conditions include
  - Severe systemic ventricular dysfunction
  - Fontan circulation
  - Cyanosis
  - Pulmonary hypertension
  - Left heart obstruction
  - Mechanical valve.
- Premature birth, neonatal death, preeclampsia, and PPH are more common in patients with ACHD.
- Multidisciplinary planning, fetal monitoring, and backup plans for maternal or fetal instability are necessary for anesthesia during pregnancy.
- Bypass cases should maintain MAP >70 mmHg and high flows for fetal protection.
- Anticoagulation during pregnancy is problematic, with LMWH preferable to warfarin
- Vaginal delivery is preferred; neuraxial techniques can be utilized with careful titration and hemodynamic monitoring.

Table 20.3 Neuraxial anesthetic dose recommendations for cesarean delivery in CHD patients

	Mild-moderate CHD		Severe CHD (mWHO III-IV)	
	Spinal/CSE	**Epidural In-situ**	**CSE**	**Epidural In-situ**
Local Anesthetic	12 mg (1.6 mL 0.75%) hyperbaric bupivacaine	2% lidocaine with 1:200,000 epinephrine and sodium bicarbonate (total 20 mL)[a]	*Intrathecal*: None, or up to 5 mg 0.75% hyperbaric bupivacaine *Epidural*: 2% lidocaine with 1:200,000 epinephrine and sodium bicarbonate (total 20 mL)	2% lidocaine with 1:200,000 epinephrine and sodium bicarbonate (total 20 mL)
Local anesthetic administration	Single shot	Bolus 5 mL increments of LA until a T4 level obtained (may take 15–20 mL)	Bolus 2–3 mL increments of LA every few minutes with careful attention to hemodynamics until a T4 level obtained (may take 15–20 mL)	Bolus 2–3 mL increments of LA every few minutes with careful attention to hemodynamics until a T4 level obtained (may take 15–20 mL)
Opioid	10–15 mcg Fentanyl, 0.15 mg PF morphine (Intrathecal)	100 mcg Fentanyl (with initial bolus) 2–3 mg PF morphine (after delivery)	10–15 mcg Fentanyl, 0.15 mg preservative free morphine (Intrathecal)	100 mcg Fentanyl (with initial bolus) 2–3 mg PF morphine (after delivery)
Fluids	Preload or co-load with 1L warm crystalloid	As clinically indicated during surgery	Use caution with pre-load or co-load. If given, consider lower volume (250–500 mL) given over 30–60 minutes	As clinically indicated during surgery
Pressor/inotrope	Phenylephrine infusion 0.5 mcg/kg/min at time of intrathecal injection. Can be weaned off after baby is delivered	Phenylephrine bolus as needed	• If intrathecal LA used: phenylephrine infusion 0.5 mcg/kg/min at time of intrathecal injection. • In patients with severely reduced EF, consider epinephrine or dobutamine (2–3 mcg/kg/min) at the time of delivery. Can be weaned off by the end of surgery	• Phenylephrine or epinephrine bolus as needed. • In patients with severely reduced EF, consider epinephrine or dobutamine (2–3 mcg/kg/min) at the time of delivery. Can be weaned off by the end of surgery

Abbreviations: LA= Local anesthetic; PF= preservative free; EF= Ejection fraction

[a] In a 20 mL syringe, mix 18 mL 2% lidocaine + 2 mL bicarb (1 meq/mL) + 100 mcg epinephrine (0.1 mL of 1 mg/mL epi)

Table 20.4 Hemodynamic effects of common uterotonic medications

	Class	CV effect	Special considerations
Oxytocin	n/a	With rapid IV bolus: • Vasodilation • Hypotension • Tachycardia • Myocardial ischemia (rare)	Safest when given as a slow bolus (<2 units/min) or a continuous infusion (18–36 units/hour)
Methergine	Ergot alkaloid that increases smooth muscle contraction	• Hypertension • Coronary vasospasm (rare) • Myocardial ischemia (rare)	• Dose: 0.2 mg IM • Avoid in patients with hypertension, preeclampsia, severely reduced systemic ventricular function, aortopathy, L→R shunts
Carboprost	Prostaglandin F2 alpha analogue	• Bronchoconstriction • Increased pulmonary artery pressure	• Dose: 0.2 mg IM • Avoid in patients with reactive airway disease, shunt lesions, right heart dysfunction, pulmonary hypertension
Misoprostol	Prostaglandin E1 analogue	None	• Safe for patients with CHD • Administered via sublingual, rectal, or vaginal routes
Tranexamic acid	Antifibrinolytic	• None shown over control groups in WOMAN trial	• Dose: 1 g over 10 minutes, repeat in 30 minutes if bleeding continues

Abbreviations: IM = intramuscular

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Adults with down syndrome

Down's syndrome is the most common chromosomal disorder, with an incidence of 1 in 700 live births in the United States each year [94]. Due to advances in congenital heart surgery and respiratory disease care, most Down's patients reach adulthood, with a median life expectancy of 58 years [95]. de Graaf et al. estimated the Down's syndrome population in the United States to be about 200,000 with a growing adult component and stabilized pediatric due to elective terminations. Around 40–50% of Down's syndrome patients have CHD, most commonly AV canal defects (37%) [10]. Hospitalization rates in the United States, using the Nationwide Inpatient Sample from 1998 to 2009 for adults with and without Down syndrome aged 18–64 years, revealed that 11.5% of all hospital admissions (9,088/78,793) for CHD were patients with Down syndrome. Patients with Down syndrome had higher in-hospital mortality (odds ratio 1.8) and were less likely to have cardiac procedures or surgery (odds ratio 0.3) [96]. Down syndrome patients in this study were also more likely to have cyanosis, secondary polycythemia, heart failure, and pulmonary hypertension. Co-morbidities include deficiencies in cognition and a tendency toward infection. Dementia may occur as early as 40 years, and the prevalence of dementia is 50–70% at 60 years. Other issues include acquired mitral valve disease, atlanto-axial instability, obstructive sleep apnea syndrome (OSAS), hearing loss, diabetes, osteoporosis, and epilepsy [97].

The preoperative visit must include a thorough history, assessment of atlanto-axial instability with recent flexion and extension views of the cervical spine and risk assessment for OSAS. Increasingly, the indication for intervention is the decrease in functional capacity, and the cardiac function should have an objective assessment to ascertain whether the cause is cardiac or onset of dementia. In the normal population, the onset of dementia is heralded by a change in memory, whereas in Down syndrome, it is often a behavior change. The plan for induction and emergence of anesthesia should involve caregivers available and interested. In patients with the unstable cervical spine, videolaryngoscopy is beneficial since it produces less upper cervical spine motion [98]. The disposition should be to areas that advanced respiratory support can be provided, such as continuous positive airway pressure (CPAP) [99].

Psychological issues

As outlined in the introduction, many patients with ACHD are lost to follow-up because they feel well and perceive themselves as an average person who had heart problems in childhood that were "fixed." In addition, many patients will have parents in attendance who are well versed in the history of their adult child's health and may have difficulty taking a secondary supportive role in decision-making. This issue is genuine if a spouse is designated as the substitute decision-maker for the patient, should they encounter a prolonged length of stay in the cardiovascular ICU. While empowering the patients with ACHD, sensitivity to these issues is an essential consideration in discussing high-risk procedures.

There is a wealth of literature addressing the psychological well-being, quality of life, and life satisfaction of adults living with CHD. In a prevalence study, Khanna et al. showed that 33% of the patients with ACHD were diagnosed with a mental illness. The most common conditions were mood disorders (13%), anxiety disorders (13%), and substance-related disorders (6%) [100]. More complex lesions requiring more interventions, and the presence of a congenital syndrome increased the likelihood of mental illness.

When the quality of life is measured about psychosocial, occupational, and environmental aspects, they are as happy as, or happier than, the public [101]. Another study found that patients with ACHD were more resilient than the general population [102]. Interestingly, quality of life does not correlate to CHD subtype, cyanosis, personal resources, or family environment [68]. These studies are done in an outpatient setting and not in the context of hospital admission with a change in health status. One in four patients with ACHD will die from heart failure. Diminished quality of life in patients with heart failure correlates with female sex and younger age, and it seems reasonable to experience depression and frustration at not being able to do activities [103]. As more patients with ACHD present for transplant or palliation, this will need to be addressed by ACHD multidisciplinary teams.

The anesthesiologist-intensivist, as a multidisciplinary team member, must ensure that the patient has a clear understanding of the anesthetic risks and the implications for their quality of life. In addition, the patient needs to have realistic expectations of how the intervention will improve their activities of daily living and exercise tolerance and over what time frame. Frank and explicit discussion of the role of the substitute decision-maker in the presence of the patient and the substitute decision-maker should ideally occur in advance of the procedure, with an opportunity to review questions should they arise before the morning of the intervention or surgery. At times, psychological counselling may be offered to help the patient through this process and support them in communicating their wishes for limits of care to their families.

Cardiac lesions

Lesions in this section are discussed in detail in individual chapters but are focused on pediatric congenital cardiac patients. This section will concentrate on the unique consideration for the patient with ACHD in both cardiac surgery and noncardiac surgery, starting with general reviews followed by lesion-specific discussions. There will be a brief discussion of the anesthetic issues unique to the adult for each of these lesions: ASDs, levo-transposition of the great arteries (L-TGA), and Ebstein's anomaly. Bicuspid aortic valve and the associated aortopathies are managed in adult practices independent of referral ACHD centers and will not be described here

Atrial septal defects and Shunts

Patent Foramen Ovale (PFO)

The foramen ovale is an essential component of fetal circulation. Generally, there is an abrupt reversal of the interatrial pressure gradient at the time of birth, allowing functional closure of the foramen ovale. Thus, anatomic closure occurs during infancy in most populations, but in up to 25%, closure is incomplete, and a potential inter-atrial communication exists into adulthood. It is possible to miss a PFO only by color flow Doppler. A contrast study (agitated normal saline injection, or agitated blood: saline in a 1:10 ratio) increases the sensitivity

of TEE. The contrast medium injected during the Valsalva maneuver is released when contrast is visualized within the right atrium to exploit the reversal of inter-atrial pressure gradients maximally. To further increase the sensitivity of the test injecting via a lower-body vein, the Eustachian valve preferentially directs blood from the inferior vena cava (IVC) toward the inter-atrial septum. The surgeries in which intraoperative closure of the PFO is almost mandatory are right-sided open-heart surgery on the beating heart and those clinical scenarios in which altered loading conditions produce a significant right-to-left shunt postoperatively. Those settings include heart transplantation, where right atrial pressure increases significantly, and implantation of a left ventricular assist device (LVAD) considerably offloads the left heart [104]. Thus, a PFO at cardiac surgery is not unique to congenital cardiac anesthesia, although it is a remnant of the fetal circulation.

Atrial Septal Defects (ASDs)

An ASD is one of the most common forms of CHD, representing 7% of CHD in childhood and 30–40% in adulthood. There are four types of ASDs. These are well described in Chapter 26 but warrant discussion as ASD is one of the lesions commonly present in the adult.

1. Secundum ASD is the most common type of defect, representing 75% of ASDs. It may be associated with mitral valve prolapse.
2. Ostium primum type ASDs are considerably less common, comprising 15% of cases. They are considered a form of AV canal defect and may be associated with a cleft anterior left AV valve leaflet or, less commonly, a cleft in the septal leaflet of the right AV valve.
3. Sinus venosus defect represents 10% of septal lesions. The superior vena cava (SVC) type of sinus venosus defect is considerably more common than the IVC type, and both types are associated with partial anomalous pulmonary venous return (PAPVR). Pulmonary venous drainage results in a left-to-right shunt. Chronic right-sided volume overload may lead to pulmonary hypertension, which is more common in patients with two veins with anomalous return or other associated conditions, such as ASD [105].
4. Coronary sinus type ASD is rare and results from unroofing the coronary sinus into the left atrium (LA), such that blood may drain from the LA to the RA via the coronary sinus. It is essential to identify an associated left-sided SVC, because of the risk of inadvertent systemic delivery of retrograde cardioplegia and the possibility of a relatively small SVC and its implications for bicaval cannulation.

Unrepaired ASDs first presenting in adulthood is associated with new-onset fatigue, arrhythmias, cerebrovascular events, or an incidental murmur during routine physical examination. Secundum ASDs represent the most common form of ASD, and large shunts (Qp: Qs >1.5:1) require closure unless severe pulmonary hypertension has developed. The contraindication for closure is the systolic PA pressure >2/3 of systemic systolic pressure or PVR >2/3 of SVR. Percutaneous device closure is the preferred technique, although significant defects or without an adequate septal rim need surgical closure. At specialized ACHD centers, nonsecundum ASDs should be repaired. A large single center series of 784 patients having ACHD surgery over a period 2004–2015 had 167 patients with septal lesions repaired, and none experienced the composite adverse outcome of death, acute kidney injury and or prolonged ICU stay, and survival to 1 year was 100% [106].

Created shunts and fenestrations

Many adults underwent Potts and Waterston shunting during childhood. The Potts shunt extends from the descending aorta to the left PA, while the Waterston shunt extends from the ascending aorta to the right PA. These shunts increase blood flow to the ipsilateral lung, over time leading to unilateral pulmonary hypertension that cannot be estimated with a simple TR jet to calculate RV systolic pressure. The original BT and modified BT shunt with a Dacron conduit from the subclavian artery to the ipsilateral PA can also cause unilateral pulmonary hypertension and differential left and right lung flow. BT and modified BT shunts decrease arterial pressure, which may, in turn, lead to diminished growth in the ipsilateral arm. Removal of the shunt during repair procedures in childhood often leads to restoring blood flow to the arm. When assessing a patient with a prior systemic artery to PA shunt for noncardiac surgery, remember to consider the patient's position while asleep, thoracotomy, nephrectomy, prone, and whether there is differential blood flow to each of the lungs. Ask the patient if they prefer to sleep in one position, check the blood pressure in both arms, assess the patient in the surgery position for 5 to 10 minutes with oximetry. Examples of surgically created fenestrations include defects in the interatrial septum during Ebstein's anomaly repair or in a Fontan tunnel wall or conduit wall. These "pop-off" valves shunt when there is inadequate RV function/compliance. However, they are also potential sources of right-to-left shunting and paradoxical emboli.

Noncardiac Surgery in Septal Lesions

The size and direction of the shunt depend on the balance between PVR and SVR. Reducing PVR (hyperoxygenation and hyperventilation) and increasing SVR (vasopressor use) can increase left-to-right shunting, leading to pulmonary overperfusion and reduced systemic blood flow. Although such changes do not lead to cyanosis, patients will exhibit reduced cardiac output. Conversely, in patients with cyanosis, increasing PVR or decreasing SVR will exacerbate the right-to-left shunt and worsen hypoxemia without decreasing systemic cardiac output. Thus, the anesthesiologist must be adept at manipulating PVR and SVR. Generally, one should strive to maintain the patient's baseline oxygen saturation level, heart rate, and blood pressure in their ambulatory life when they are well.

KEY POINTS: ATRIAL SEPTAL DEFECT, SHUNTS, AND PAPVR

- PFO should be closed if symptomatic and during surgery for other defects.
- Secundum ASD is the most common type; pulmonary vascular disease is rare
- PAPVR is commonly associated with sinus venosus ASD and must be repaired by patch-baffle at the time of ASD surgery.
- Assess patients with systemic to PA shunts with a mind to the surgical positioning and differential pulmonary blood flow.

Ventricular septal defect (VSD)

A VSD is the most common congenital cardiac lesion in the adult population, excluding the bicuspid aortic valve, with a prevalence of 0.3 per 1,000, representing around 10% of ACHD. The anatomical considerations and classification of VSDs are described in detail in Chapter 26. Briefly,

i. Membranous defects, located in the membranous septum, are associated with TOF and abnormalities of the septal leaflet of the tricuspid valve. They are the most common defects (70%).
ii. Inlet VSD is located between the mitral and tricuspid valves and represents a form of endocardial cushion defect, and as such, may be associated with primum ASD and cleft mitral valve.
iii. Outlet, supracristal, or infundibular lesions are located just below the semilunar valves and are associated with prolapse of the right coronary cusp of the aortic valve and AI.
iv. Muscular VSDs may be congenital or acquired, single or multiple, and minor defects frequently close spontaneously in childhood.

The hemodynamic significance of a VSD depends on several factors: the size of the defect, the pressure gradient across the VSD, and the PVR. An isolated VSD will initially facilitate left-to-right shunting, which will significantly increase pulmonary blood flow in those VSDs with higher shunt volumes. Over time, this increased flow may result in changes in the pulmonary vasculature, which may lead to elevations of PVR, and eventually shunt reversal and Eisenmenger physiology. The anesthetic considerations for these various hemodynamic concerns are discussed in Chapter 26. The risk of endocarditis for all patients is not insignificant, even those with minor defects, and patients should receive prophylaxis according to current guidelines [10].

Outside of the developing world, most patients who reach adulthood with unrepaired VSDs have small lesions of little hemodynamic significance. Indications for repairing these lesions include Qp:Qs >1.5–2:1, evidence of LV volume overload, elevated PVR, or abnormalities of surrounding structures (such as aortic regurgitation in an outlet or infundibular VSD). Surgical correction traditionally occurs via a right ventricular approach, and, as such, conduction disturbances are common postoperatively. Multiple "Swiss cheese"-type muscular VSDs may be technically challenging repair and present for PA banding or hybrid approach instead [107].

Patent ductus arteriosus

A small PDA may present in adulthood for the first time with a left-to-right shunt and subsequent LV volume overload, dilation, and failure. General principles relating to patients with left-to-right shunts should be applied, as discussed earlier. Eisenmenger syndrome may eventually develop, resulting in the disappearance of the classical "machinery" murmur and differential clubbing and cyanosis of the lower limbs only [108].

Coarctation of the Aorta

Aortic coarctation is frequently associated with the bicuspid aortic valve, PDA, and mitral valve abnormalities. LV pressure overload results in concentric LV hypertrophy and diastolic dysfunction. Arterial hypertension occurs in the upper limbs, with relative hypotension in the lower limbs. More severe coarctation may result in the development of collateral vessels to maintain distal perfusion. In addition, longstanding hypertension results in accelerated coronary artery disease, risk of stroke, and aortic dissection.

Although aortic coarctation is frequently stented or repaired in childhood, it may recur in adulthood. Aneurysm formation may also be a late complication of repair. Less commonly, a patient may present for the first time in adolescence with upper body hypertension. Over the past decade, stenting is the technique of choice for primary, recurrent coarctation in adults and, in some instances of aneurysms [109, 110]. Guidelines suggest intervention when the gradient exceeds 20 mmHg or when proximal hypertension is explained by the narrowing, even if the gradient is <20 mmHg. In some cases, open repair is required. The approach is via left thoracotomy and requires lung isolation and collapse of the left lung. The presence of well-developed collaterals will prevent excessive proximal hypertension on clamping of the aorta. Left heart bypass or circulatory arrest is needed to intervene in the aorta. This procedure requires detailed planning and a team accustomed to lung isolation. Postoperatively, hypertension is common and may persist. Open repair of coarctation or aneurysm that is periductal is well within the skill set of a cardiac anesthesiologist in adult-acquired practice where acquired thoracic aneurysms are repaired.

Pulmonary valve stenosis (PS)

Pulmonary stenosis is a relatively common lesion, representing approximately 8–10% of all CHD lesions. It may occur as an isolated phenomenon, associated with other defects such as ASD, VSD, or PDA, or as part of the constellation of features of TOF (see later). The stenosis is most commonly at the valve level but may also be supravalvular or subvalvular. Valvular PS is associated with Noonan syndrome. Supravalvular PS may occur in association with Noonan, DiGeorge, and congenital rubella syndromes.

Although many patients with more severe lesions present and are treated in the neonatal period or early childhood, a proportion of patients with the milder disease will remain asymptomatic until adulthood. In these patients, indications for intervention include right ventricular outflow tract (RVOT) gradient >64 mmHg, symptomatic PS, decreased RV function, double-chambered RV (RV chamber divided in two by anomalous muscle bands), significant arrhythmias, ASD or VSD with right-to-left shunting [111]. Balloon valvuloplasty is generally the first-line treatment. However, patients with more complex anatomy, infra-valvular stenosis, or additional associated defects require surgical repair. Open repair typically takes the form of open valvulotomy with or without a transannular patch. Valve replacement rarely is the initial surgical treatment.

In adulthood, patients who have previously had interventions for PS frequently present either recurrent stenosis or hemodynamically significant pulmonary regurgitation (see Figure 20.6). Therefore, intervention is indicated in all cases of symptomatic pulmonary regurgitation and an objective decrease in exercise capacity, progressive RV dilatation, RV systolic dysfunction, tricuspid regurgitation, or sustained atrial or ventricular dysfunction arrhythmias.

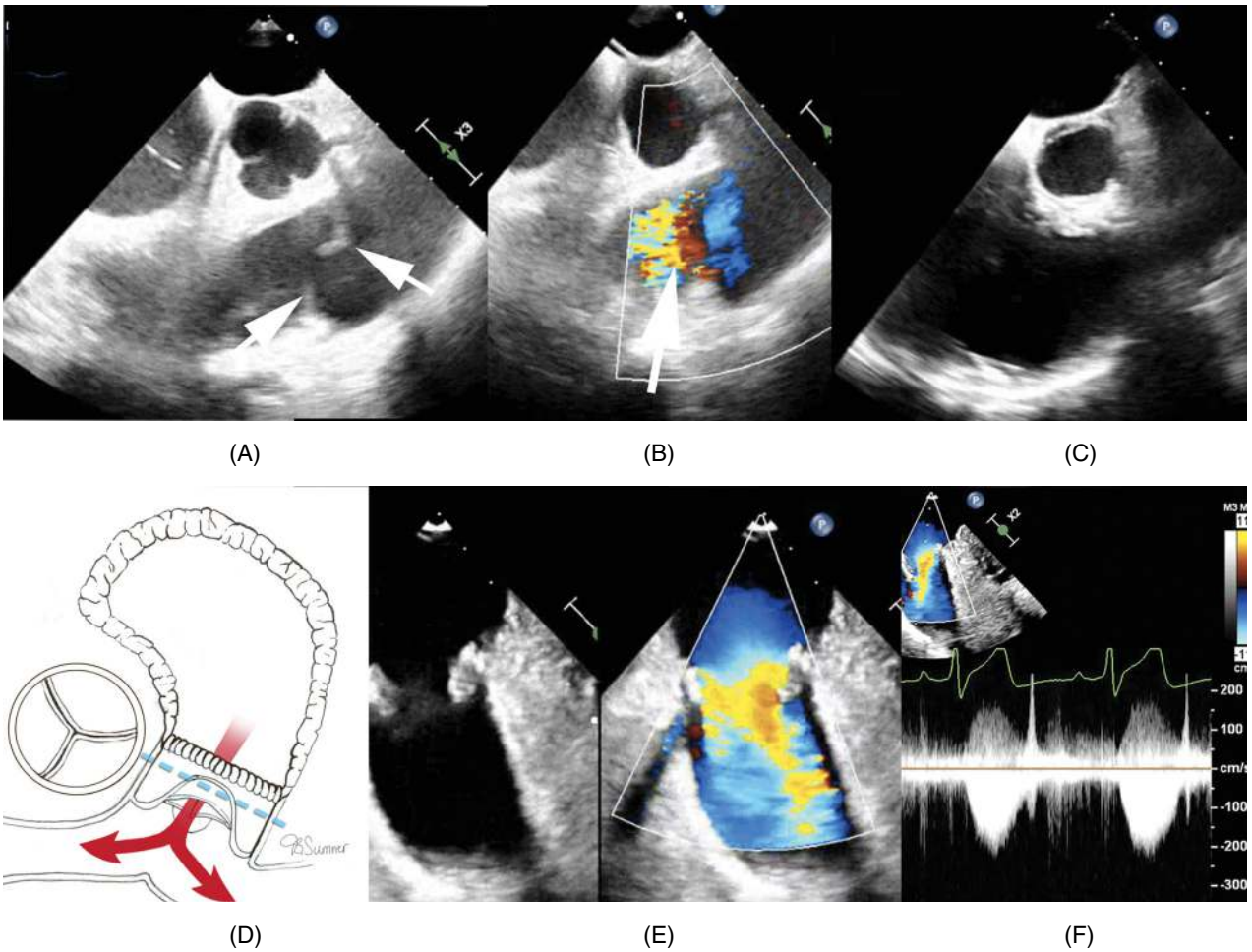


Figure 20.6 Preoperative TEE of an adult patient with congenital PS post balloon dilation palliation as an infant presenting with severe PI for PV replacement; (A) Mid esophageal RV inflow and outflow view showing dysplastic pulmonary valves with lack of coaptation (white arrow); (B) same view with color flow Doppler displaying free PI (white arrow); (C) post CPB RV inflow outflow view with poor visualization of the PV; (D) illustration exhibiting the replaced pulmonary valve in caudal view; (E) epicardial echocardiography showing the PV replacement with 29 mm Epic St. Jude tissue valve 2-D and color flow Doppler; (F) same view color flow Doppler displaying mild flow acceleration across the pulmonary valve, peak 2.2 m/s and trivial regurgitation. Abbreviations: TTE, transesophageal echocardiography; PS, pulmonary stenosis; PI, pulmonary insufficiency; RV, right ventricle; CPB, cardiopulmonary bypass. Source: Reproduced with permission from Texas Children's Hospital.

Percutaneous pulmonary valve replacement or transcatheter pulmonary valve implantation

Percutaneous pulmonary valve replacement was introduced in the early 2000s with the original case reported by Bonhoeffer in a 12-year-old with a stenotic RV to PA conduit [112]. Initial indications were in dysfunctional RVOT and RV to PA conduits. It has expanded to patients with PS or PI with previous transannular patches in their original repair and valve in valve stented tissue bioprosthetic valves. There are two commonly available balloon-expandable valves, the Melody® valve (Medtronic, Minneapolis, MN, USA), a bovine internal jugular valved conduit sewn over a bare metal platinum–iridium stent, and the Sapiens valve (Edwards Lifesciences Corp., Irvine CA, USA), a bovine pericardial valve mounted on a cobalt-chromium alloy frame. Although the morbidity and mortality for surgical pulmonary valve replacement is less than 1% in most series, the mortality is far less in the percutaneous approach, albeit with an increase in post-procedural right-sided endocarditis [113–115]. Table 20.5 describes the transcatheter heart valve size recommendations and clinical cases are showed in Figures 20.7 and 20.8.

TOF, pulmonary atresia with an RA to PA conduit, and pulmonary homograft dysfunction post-Ross procedure are all common reasons for a TPVRI. Although the patients have a much-reduced length of stay in the hospital, there is a need for careful planning, assessment of comorbidities, a contingency plan for urgent open repair, and a post-procedural monitored environment. Deep anesthesia with muscle relaxation while deploying the percutaneous valve is desirable to avoid coughing with balloon dilation causing pulmonary hemorrhage, manifesting as a pulmonary hemorrhage, or mal-deployment/embolization. Complications also include fracture of the conduit/stent, failure to deploy due to too large an annulus, and damage to the tricuspid valve. The pulmonary valve annulus is close to the left main coronary artery, and compression can manifest with ventricular ectopy, ischemic changes in the electrocardiogram, and wall motion abnormality [116, 117].

Table 20.5 Transcatheter Heart Valve size recommendations are based on native valve annulus size, as measured by transesophageal echocardiography, or computed tomography

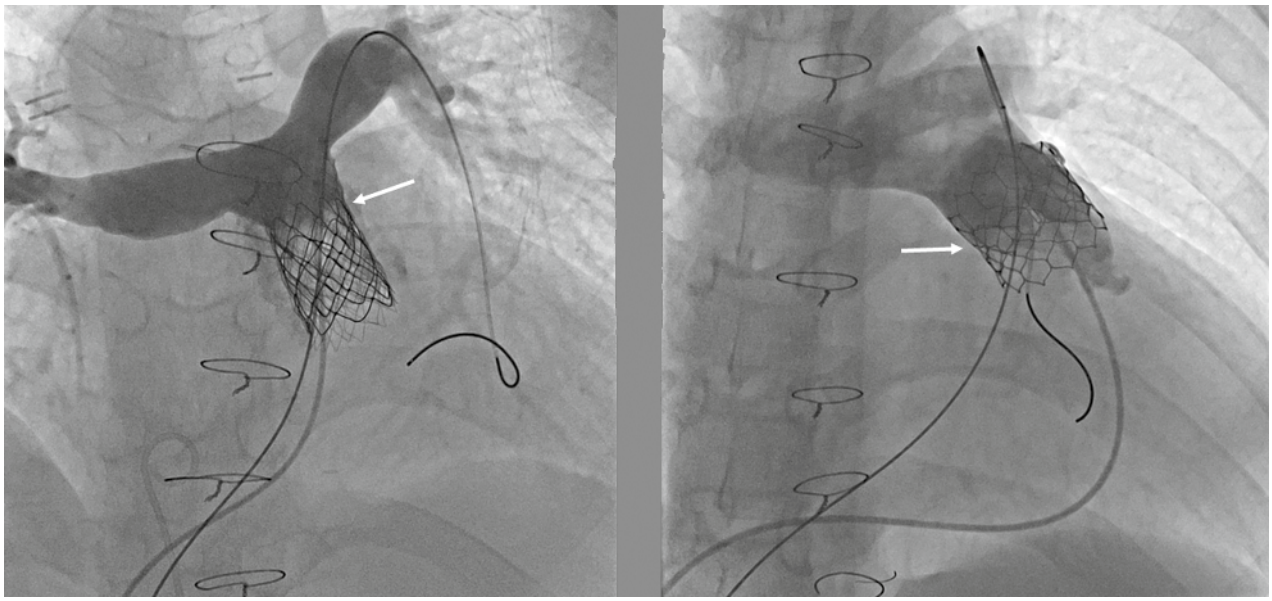
Transcatheter valve type	THV Size (mm)	Native valve annulus size by TEE/CT (mm)
Melody valve	20	Up to 20
(Medtronic)	22	Up to 22
SAPIEN 3	20	16–19
(Edwards)	23	18–22
	26	21–25
	29	24–28

Abbreviations: THV, Transcatheter Heart Valve; TEE, transesophageal echocardiography; CT, computed tomography.

Tetralogy of Fallot

TOF is the most common repaired cyanotic defect in the ACHD population, and these patients frequent the electrophysiology laboratory, urgent and emergent cardioversion lists, interventional suite for percutaneous valve and branch PA dilatation, and the operating room for pulmonary valve replacement, RVOT plication/remodeling and tricuspid valve repair/annuloplasty. Rarely does an adult present for primary correction in the developed world. Most older adults will present for a re-intervention or surgery, having had a palliative systemic-to- PA shunt for cyanosis followed by a repair as a child. Younger adults were likely diagnosed in utero and had medical therapy in the first few weeks to months of life and subsequent correction at 3–6 months [118, 119]. Most patients will have had a transannular patch to widen the RVOT at the time of repair, and over time they will develop pulmonary insufficiency, RV dilatation, and eventually tricuspid regurgitation due to RV dilatation. A smaller percentage of adults will have restriction of their RVs, which correlates with having had a transannular patch, elevated troponins immediately after repair, inotropic requirements, and prolonged time in the ICU. The restriction appears to protect the RV from ventricular dilatation due to pulmonary insufficiency [120]. The optimal timing of a pulmonary valve replacement with or without an RV plication and a tricuspid valve annuloplasty has been challenging to define, but a consensus amongst reference centers is forming. Intervening before RV end-diastolic volumes of 160 mL/m^2 or end-systolic volumes of 80 mL/m^2 and before QRS duration reaching 180 ms suggest improving RV remodeling and reducing the risk of sustained ventricular tachycardia, atrial arrhythmias, and sudden death [121].

The burden of arrhythmias for adult TOF is substantial, both atrial and ventricular, along with a lifelong risk of sudden death. A multi-institutional cross-sectional study found at least one type of clinically sustained arrhythmia in 79% of TOF patients >18 years with a median age of 36 [120]. Atrial arrhythmias, flutter, and fibrillation, correlate with tricuspid regurgitation and older age of repair. Ventricular arrhythmias and sudden death correlate with increased QRS duration and repair at an older age. The assessment of RV function and mass by magnetic resonance is now the gold standard. A multicenter registry, the INDICATOR cohort, of TOF adults has shown that RV hypertrophy, RV dysfunction, and LV dysfunction are defined by magnetic resonance correlate with sustained ventricular tachycardia [122]. Similarly, a report from the INDICATOR cohort post adult pulmonary valve replacement found 8% patients experienced sudden



(A) (B)

Figure 20.7 Fluoroscopic images of percutaneous pulmonary valve replacement; (A) ACHD patient with TOF and significant RV-PA conduit stenosis and regurgitation underwent RV-PA conduit stenting and then Melody® valve (Medtronic, Minneapolis, MN, USA) placement in the RV-PA conduit, a wide RV-PA conduit can be seen with no significant regurgitation through the Melody® valve (white arrow); (B) Another ACHD patient with significant pulmonary regurgitation and right ventricle volume overload underwent placement of an Edwards Sapien 3 transcatheter heart valve (Irvine, CA) with no significant regurgitation seen after valve deployment (white arrow).

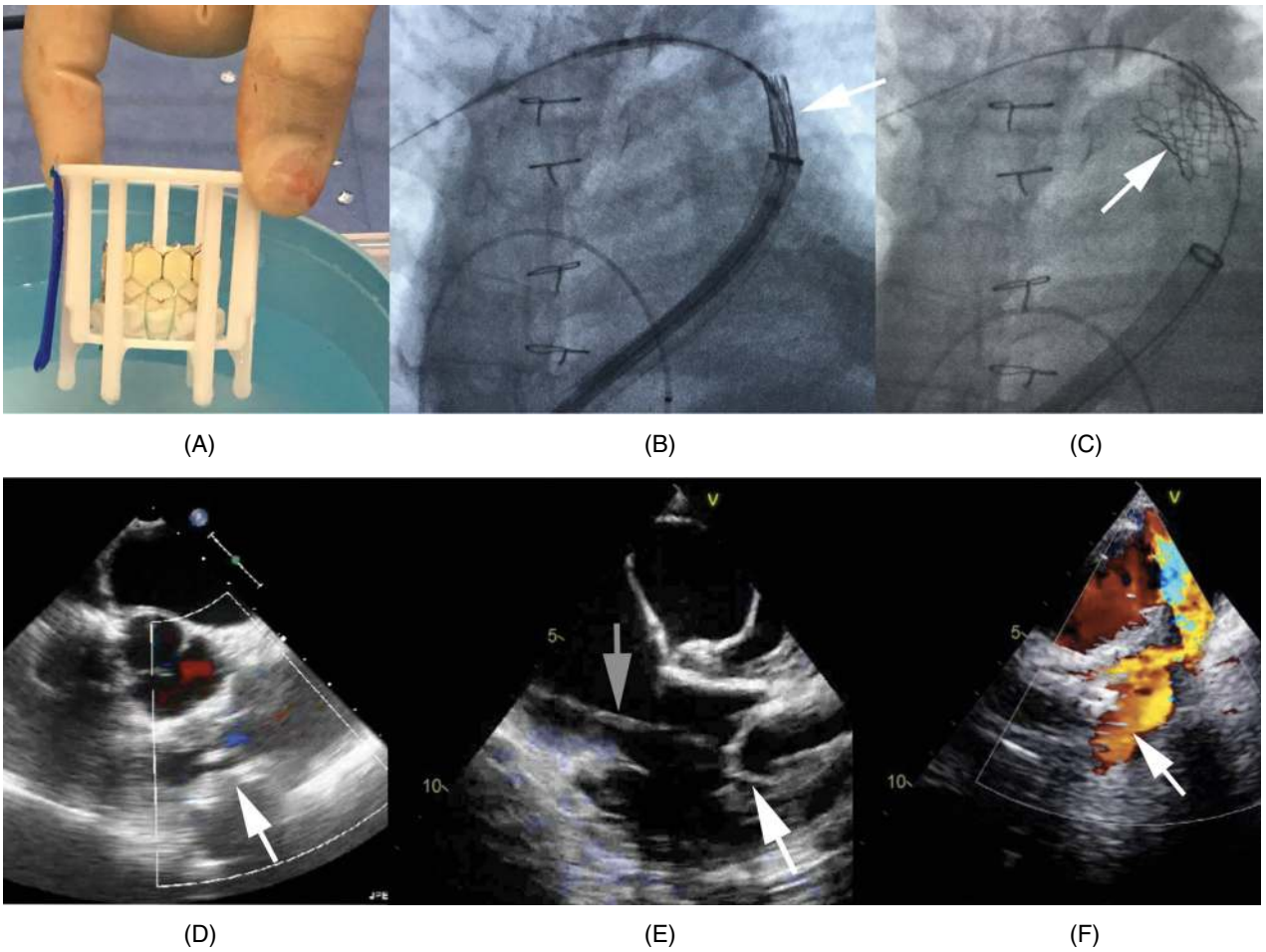


Figure 20.8 Images of the percutaneous insertion of an Edwards Sapien 3 PV transcatheter heart valve (Edwards Lifesciences Corp., Irvine, CA, USA); (A) Edwards sapiens 3 valve size 26 mm; (B) anteroposterior fluoroscopic view pre valve deployment visualizing the valve on the deploying sheath (white arrow); (C) same fluoroscopic observation with the deployed PV in the RVOT (white arrow); (D) post deployment TEE mid esophageal RV inflow and outflow view showing competent PV with trivial PR (white arrow); (E) same TEE window showing a prolapsed percutaneous pulmonary valve in the RV (white arrow) and the deployment sheath through the TV (gray arrow); (F) Color flow Doppler of the prolapsed PV with severe PR (white arrow). Abbreviations: PV, pulmonary valve; RVOT, right ventricular outflow tract; TTE, transesophageal echocardiography; RV, right ventricle; PR, pulmonary regurgitation.

death or sustained ventricular tachycardia post pulmonary valve replacement with a median follow-up of 6.5 years, older age at PVR and pre-PVR RV hypertrophy, and dysfunction was predictive of shorter time to postoperative death and sustained VT [122].

Arrhythmia, electrophysiology, and diagnostic procedures

Symptomatic atrial arrhythmias, ventricular tachycardia, and catastrophic ventricular tachycardia/ventricular fibrillation are essential to the anesthesiologist as the hemodynamic considerations of TOF. The adult cardiac anesthesiologist will experience an increasing exposure to TOF patients for electrophysiological mapping, ablation, and insertion of prophylactic defibrillators. The management of hemodynamics depends on the predominance of stenosis or regurgitation of the pulmonary outflow tract. Patients with hypokinetic dilated RV due to pulmonary regurgitation will benefit from spontaneous ventilation and afterload reduction. Those with residual outflow tract gradients will need adequate preload.

Cardiac surgery

Management of the adult TOF patient for a pulmonary valve replacement with or without RV plication, tricuspid valve annuloplasty, or cryoablation is the most common surgical procedure in the Society of Thoracic Surgeons' database with a low <1%, 30-day mortality in a referral center for ACHD surgery. The hemodynamic goals must focus on maintaining RV contractility, minimizing PVR, and avoiding arrhythmogenic triggers. Intravenous and inhalational agents that diminish contractility have minimal effects on the PVR and minimal arrhythmogenic potential. Ventilation should be at or close to FRC, with minimal positive end-expiratory pressure (PEEP), and converted to a spontaneous ventilation mode, when possible, once in the postoperative or ICU setting. Along with recognizing the detrimental effects of long-term pulmonary

insufficiency and RV dilatation due to transannular incisions, adult anesthesiologists will see an increasing number of young adults with residual stenosis and outflow tract obstruction for both the operating room and catheterization laboratory. Anticipation of and a treatment plan for both atrial and ventricular arrhythmias is essential [123].

In developed nations, adults who have unrepaired TOF frequently come from developing countries and have anatomy favorable to surviving as an adult. They will have all the anesthetic considerations of living with cyanotic heart disease, as well as the co-morbidities described previously in this chapter. The anesthetic management of an unrepaired TOF patient for definitive repair is described in Chapter 28. There are a few special considerations for the adult patients [124]. Patients who survive will likely have aortopulmonary collaterals that can be problematic in the operating room and postoperative ICU management. Preoperative coil embolization of extensive collaterals will reduce the run-off of aortopulmonary collaterals, which will lower MAP on bypass. However, the pulmonary vasculature may not be well developed, and patients will have less lung reserve. Postoperatively, the pulmonary vasculature will have a total cardiac output and additional left-to-right shunting from pulmonary collaterals, and there will be a risk of life-threatening pulmonary hemorrhage, which may require lung isolation and definitive management in the interventional suite or operating room.

Non-cardiac surgery

Management for the adult repaired TOF for noncardiac surgery will be tailored to the predominant pathology of the RV and pulmonary outflow tract as stated in the discussion of the arrhythmia, electrophysiology, and diagnostic procedures. Comorbidities resulting from living with a dilated and pressure or volume-loaded right heart such as congestive cirrhosis are needed to be evaluated in the preoperative period. Arrhythmias, both atrial and ventricular, are common, and a preemptive drill with the intraoperative surgical and nursing team at the start of the case is warranted and includes suitable placement of defibrillator pads and a test of contact before prepping. Inotropes to assist with RV dysfunction and pulmonary vasodilators may be necessary. Anesthetic techniques and post-anesthetic pain management should be mindful of keeping the PVR low. Appropriate postoperative monitoring in an ICU setting for heart failure and arrhythmia is critical.

Pulmonary atresia

Pulmonary atresia is a heterogeneous diagnosis and has three broad categories. Pulmonary atresia is the absence of direct communication between the ventricular chamber/s and the pulmonary vasculature [125]. It is classifieds as:

1. Pulmonary atresia with an intact ventricular septum is an extreme form of TOF. With an adequately sized ventricle, an intervention is an RV to PA conduit or a "two ventricle repair."
2. Pulmonary atresia with VSD patients shares the intracardiac anatomy of TOF without direct communication between the RV and the PA. These patients may have a "two ventricle repair" with the closure of the VSD and an RA to PA conduit.
3. There is a 3rd group of pulmonary atresia, VSD, and complex univentricular anatomy types with additional defects not suitable for biventricular repair. Patients may have an absence of the main PA, and extensive aortopulmonary collaterals supply the pulmonary vasculature.

The Royal Brompton group reported their experience of a large population of patients labeled as Pulmonary atresia, 227 patients, mean age 25.5 ± 8.7 years, over a median follow-up of 8.8 years. The patients represented the full spectrum described above and were categorized in one of the three groups above based on original anatomy, and group 1 was subdivided into repaired (a) and unrepaired (b). Interestingly all three groups had no difference in survival (78%) and, there was no significant difference in survival between groups between repaired and unrepaired patients [125].

Anesthetic management will depend on the anatomy and type of repair the patient has or has not had in childhood. Many will be managed like TOF with an RV to PA conduit and. Others may be complex single ventricles with aortopulmonary collaterals and segmental pulmonary hypertension and unrepaired or palliated with a Fontan circulation.

KEY POINTS: PULMONARY STENOSIS, TETRALOGY OF FALLOT, PULMONARY ATRESIA

- PS is common and may be asymptomatic until adulthood when right heart failure occurs.
- TOF is the most common ACHD repaired cyanotic defect; pulmonary valve replacement and arrhythmia treatment are common procedures
- Pulmonary Atresia is a heterogenous diagnosis and should be managed based on the original anatomy and the surgical intervention (*two ventricle repair* or Fontan)

Congenitally corrected transposition of the great arteries

L-TGA is also called congenitally corrected transposition of the great arteries (ccTGA), and this is also called congenitally corrected or L-transposition of the great vessels, terms that confuse many. The term implies that the patients are "born corrected or physiologically compatible with life." These patients have both AV discordance and ventricular-great artery (VA) discordance; the RA connects to the morphological LV that is subpulmonic; the LA connects to a morphological RV which is subaortic. L-TGA is one of the rare CHD with adult presentation that on echocardiography appears erroneously as a normal four-chamber heart; however, the RV and LV (the tricuspid valve is more apically placed).

Most of these patients have VSDs (60–80%), sub-valvular or valvular pulmonic stenosis (30–50%), and abnormalities of the systemic AV valve (up to 90%) that is described as Ebstein's-like with moderate-to-severe systemic AV valve regurgitation [126].

In the absence of associated anomalies, these patients present in the second and third decades of life with systemic AV

valve regurgitation and symptoms of heart failure. Arrhythmia is a frequent presentation, including complete heart block with increasing age and atrial arrhythmias, usually a symptom or consequence of a more significant problem such as a failing systemic RV with tricuspid regurgitation. Much like the Mustard and Senning patients (see later), they are managed like a patient with dilated cardiomyopathy and likely have a degree of PAH and may be on a transplant or mechanical assist pathway (see Figure 20.9).

Surgical interventions depend primarily on the associated anomalies. The patients with PS who have subpulmonic LVs are trained for systemic pressures and may be candidates for an atrial and arterial "double switch" operation. Patients without subpulmonic obstruction can be considered for sequential PA banding to train the LV for a potential "double switch." It is a staged process that requires multiple surgical interventions, and many patients improve with the PA band alone, which causes a septal shift due to increased LV pressures and improvement in the systemic RV geometry with less tricuspid regurgitation. This palliation may be a destination on its own, or the patient can proceed to a combined Mustard/Senning with either an arterial switch or a Rastelli procedure [127, 128]. Additional details about surgical approaches to L-TGA are presented in Chapter 29.

Dextro-transposition of the great arteries (D-TGA)

D-TGA mustard or senning baffle

Dextro-transposition of the great arteries (D-TGA) patients has atrial–ventricular concordance and ventricular–great artery discordance (see Figure 20.10). The RV is the subaortic and systemic ventricle. Although rarely done now, many adults live with atrial baffle repairs, which redirect the atrial blood to the opposite ventricle (see Figure 20.11). The Senning and Mustard operations were the standard of care, often with a prior temporizing systemic-to-pulmonary artery shunt, until the mid-1980s when the arterial switch became the preferred method. Retrospective reviews reveal the good quality of life until the fourth decade with 25-year survival

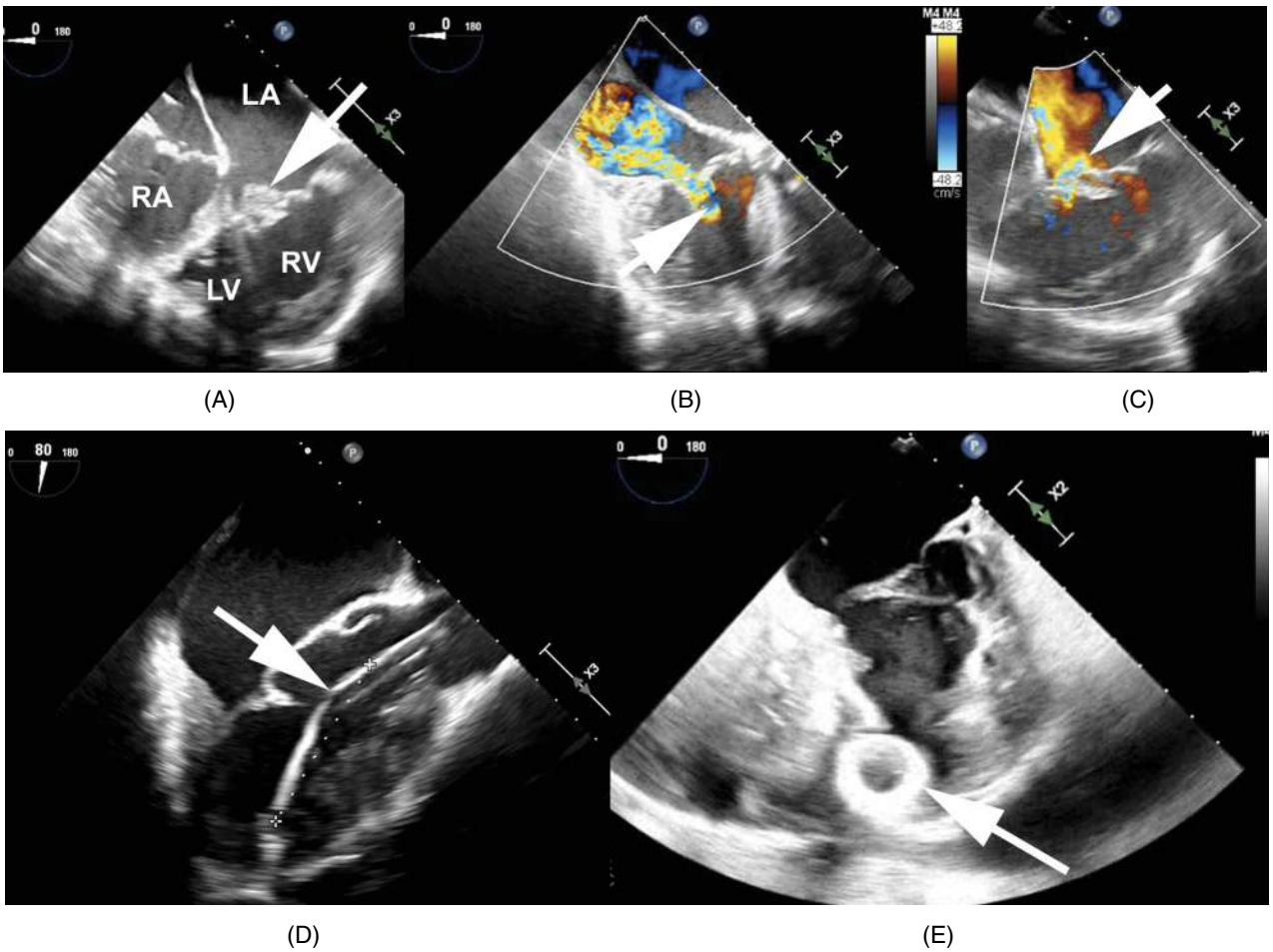


Figure 20.9 TEE images of an L-TGA patient with end stage heart failure; (A) Mid esophageal four-chamber views showing the apical displacement of the Ebstenoid TV (Systemic AV valve; (B) Same view focusing on the MV (Pulmonary AV valve) with severe MR (white arrow); (C) Identical window concentrating on the Ebstenoid TV (Systemic AV valve) with moderate TR (white arrow); (D) Mid esophageal long axis view illustrating the Impella percutaneous ventricular assist device in the 6.5 in the LV chamber (white arrow); (E) Mid esophageal four-chamber view post Heart Mate 3 ventricular assist device implantation visualizing the outflow cannula in the LV cavity (white arrow). Abbreviations: L-TGA, levo-transposition of the great arteries; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

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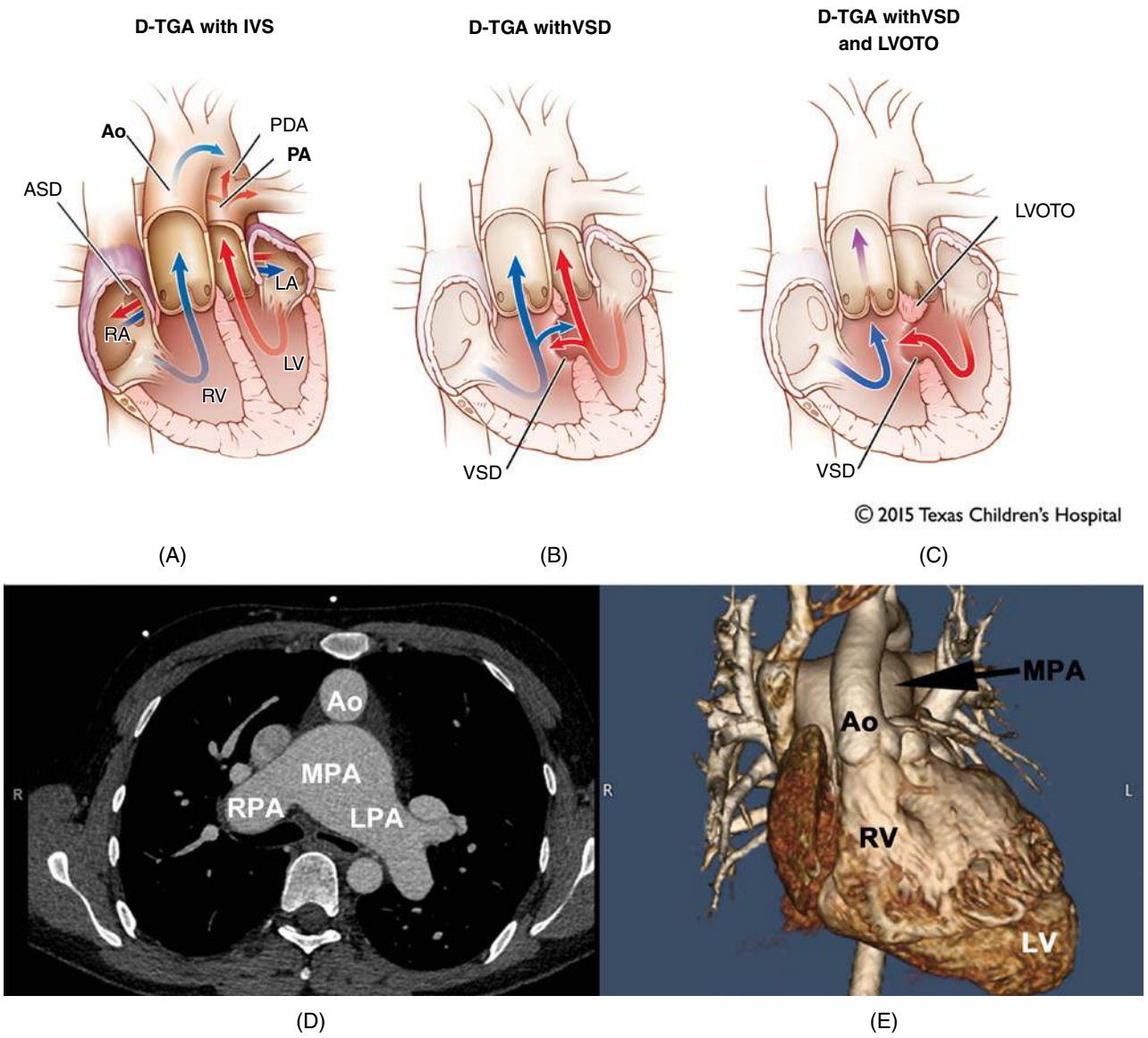


Figure 20.10 Illustrations of the three types of D-TGA presentation; (A) D-TGA with intact interventricular septum; (B) D-TGA with ventricular septal defect; (C) D-TGA with left ventricular outflow obstruction; (D) CT of an ACHD patient with unrepaired D-TGA with large ventricular septal defect and Eisenmenger syndrome, notice the anterior aorta arising from the RV and the dilated main pulmonary artery appearing posteriorly from the LV; (E) CT three-dimensional reconstruction showing the same findings. Abbreviations: D-TGA, dextro-transposition of the great arteries; ASD, atrial septal defect; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PDA, patent ductus arteriosus; Ao, aorta; MPA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery. Source: Reproduced with permission from Texas Children's Hospital.

rates of 91% in Senning) and 76% in Mustard [129]. The drawback is that the RV remains as the systemic ventricle [129]. Patients with a Mustard or Senning repair frequently have baffle leaks, obstruction or narrowing of the SVC, IVC or pulmonary veins, atrial sinus arrhythmias, sick sinus syndrome, and inevitably systemic ventricular failure with systemic (tricuspid valve) AV valve regurgitation [130].

The anatomy can appear complicated; however, there is a physiological correction. A red cell will traverse the cardiopulmonary circulation in an appropriate sequence but with reversed roles of the ventricles. Central venous access can be challenging, as the catheters may get caught up in the baffle or make an abrupt turn from the LV back to the PA. The patients are frequently pacemaker-dependent with multiple central vein manipulations in the past and narrowed SVC. Hemodynamically, D-TGA with a subaortic RV repair presents like a dilated cardiomyopathy with a failing systemic ventricle with AV valve regurgitation. Agents to promote contractility and systemic afterload reduction are the goals.

Case reports of PA banding in adults to train the subpulmonic LV for systemic pressure and subsequent take-down of the Mustard baffle and arterial switch had mixed success, with significant morbidity and mortality [131]. Adult patients may present for revision of an obstructed baffle. Far more frequently they are scheduled for pacemaker, defibrillator, and electrophysiology procedures. Cardiac transplantation is technically challenging and may not be possible due to PAH.

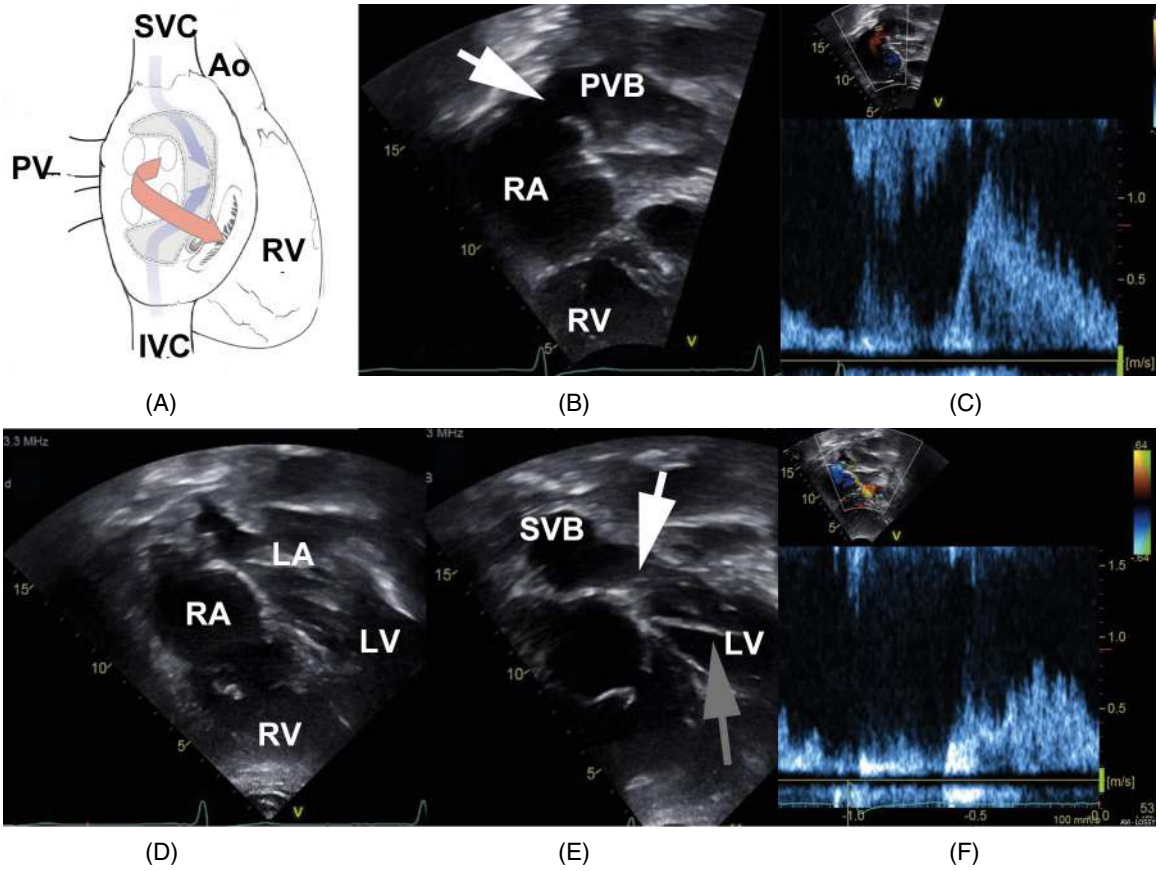


Figure 20.11 (A) Illustration of the Mustard procedure with pulmonary venous baffle to the RV (red arrows) and systemic venous baffle to the LV (blue arrows); (B) TTE echocardiography apical four-chamber view showing the pulmonary venous baffle to the RA (white arrow); (C) Pulse wave Doppler displaying unobstructed pulmonary vein baffle flow; (D) same window exhibiting moderately dilated and hypertrophied systemic RV; (E) identical view focusing in the systemic venous baffle (white arrow) with a transvenous pacemaker through the baffle (gray arrow); (F) open by pulse wave Doppler. Abbreviations: TTE, transthoracic echocardiography; PV, pulmonary veins; SVC, superior vena cava; Ao, aorta; RV, right ventricle; IVC, inferior vena cava; PVB, pulmonary venous baffle; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; SVB, systemic venous baffle.

D-TGA with an arterial switch

In the late 1970s and early in the 1980s, CHD pediatric centers moved from the Senning, and Mustard repairs to the Jatene or arterial switch operation [132]. These patients have yet to reach adult centers in large numbers. Still, complications include coronary artery perfusion defects and aneurysms of the neo-aortic root [133]. The advantage is that the LV is the systemic ventricle, with AV and VA synchrony restoration.

D-TGA with VSD and PS and a Rastelli repair

Patients with D-TGA, VSD, and PS in childhood are amenable to Rastelli repair. This procedure entails an LV tunnel through the VSD to the aorta and extracardiac conduit that connects the RV to the central PA. The systemic ventricle is the LV; however, these patients return for obstruction of their conduits. These are surgical cases with considerable risk of entry into the conduit on sternotomy in the past. Still, increasingly these patients are dealt with in the interventional suite for TPVRI and balloon dilatation of the conduit. Freedom from death or transplant at 20 years is disappointing in this population at 58% [134].

KEY POINTS: TRANSPOSITION OF THE GREAT ARTERIES

- L-TGA may be asymptomatic until adulthood; arrhythmia, including heart block and heart failure, are the usual presenting signs.
- D-TGA patients' historical treatment was Mustard or Senning intra-atrial baffling until the 1980s; problems include frequent arrhythmias and systemic RV failure.
- The arterial switch became the standard treatment for D-TGA in the late 1980s; adults may have coronary artery perfusion defects and neo-aortic aneurysms.

Ebstein's anomaly

Ebstein's anomaly is a rare anomaly, less than 1% of all CHD, characterized by apical displacement of the septal and posterior leaflets of the TV (Figure 20.12). These leaflets may lack chordae and are therefore attached directly to the ventricular wall. The anatomic change results in tricuspid regurgitation, and atrialization, and reduced functional size of the RV. The anterior leaflet of the tricuspid valve may be large and redundant, resulting

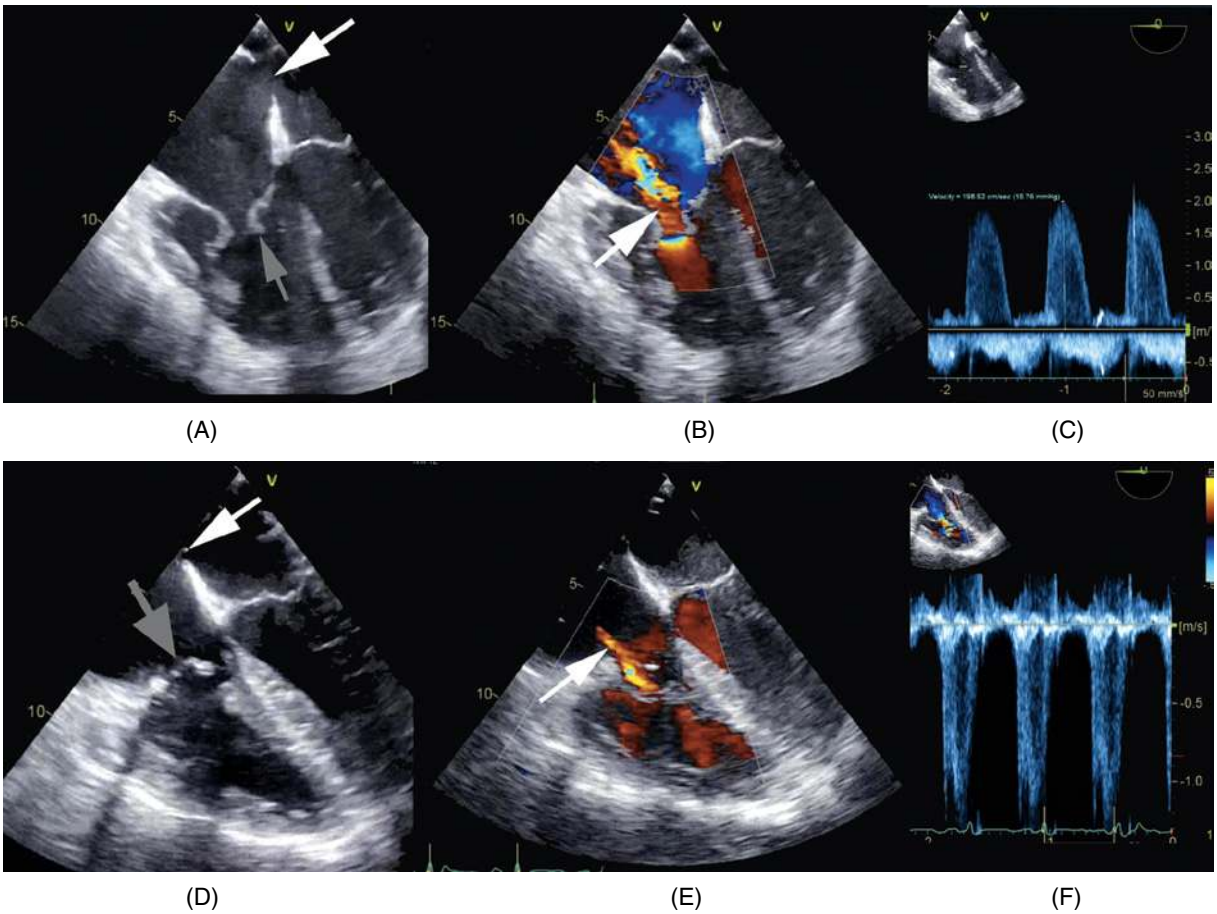


Figure 20.12 Pre-operative TEE of Ebstein's anomaly showing mid esophageal four-chamber view (A) Ebsteinoid/dysplastic tricuspid valve with apical displacement of the septal leaflet (gray arrow), lack of leaflets coaptation and large ASD (white arrow); (B) Color flow Doppler of the same view compatible with moderate-to-severe TR (white arrow); (C) Continuous wave Doppler displaying a dense jet with a peak velocity of 2.0 m/s confirming moderate-to-severe TR; Postoperative TEE post TV repair, ring annuloplasty and ASD closure at the mid esophageal four-chamber view (D) annuloplasty ring (gray arrow), small ASD (pop-off); (E) Continuous wave Doppler with trivial TF jet (white arrow); (F) Pulse wave Doppler of the TV inflow revealing mild stenosis (mean gradient of 5 mmHg) Abbreviations: TEE, transesophageal echocardiography; ASD, atrial septal defect; TR, tricuspid regurgitation; TV, tricuspid valve.

in RVOT obstruction. Ebstein's anomaly is frequently associated with other cardiac anomalies, particularly ASD. Secundum ASD occurs in over 90% of individuals [135].

Those with relatively milder disease may present for the first time in adulthood, often presenting as new onset of an atrial arrhythmia. The context may be surgical (e.g., acute cholecystitis, appendicitis) or labor and delivery. The degree of abnormality lies on a broad spectrum of natural history and severity, depending on the degree of displacement of the tricuspid valve leaflets, and the degree of shunting across a PFO or secundum ASD. The first presentation beyond the fifth decade is rare; however, patients may present as late as the eighth decade [136]. Older patients most commonly present with arrhythmias, but paradoxical embolus may occur in those with ASD or PFO.

Arrhythmia, electrophysiology, and diagnostic procedures

A European multicenter study reported 32 patients (mean age 24 ± 15 years) with atrial arrhythmia of which re-entry tachycardia was the most common (69%), previous surgery in 9 (32%), prior catheter based ASD closure in 3 (9%). More than 60% of the patients had been on a median of 2 (range 1–4) antiarrhythmics and had a median of 2 (range 1–26) previous cardioversions [137].

Several factors must consider in the management of Ebstein's. First, the amount of RV dysfunction followed by shunting at the atrial septum level. The latter could cause paradoxical emboli or reverse shunting and hypoxemia. Ideally, light conscious sedation with oxygen supplementation and avoidance of elevated $PaCO_2$.

In DC cardioversions, pre-oxygenate the patient and hyperventilate before administering hypnotics. Wait for spontaneous ventilation rather than assist positive breath manual ventilation. Be mindful that the circulation time to render the patient unconscious may be prolonged and resist the temptation to supplement with additional doses. A small dose of benzodiazepines may reduce the total quantity of propofol and lessen the drop in systemic blood pressure and the risk of shunting.

Cardiac surgery

The Cone repair was introduced by Da Silva and colleagues and adopted throughout the cardiac surgical community [138]. The repair is not exclusive to pediatrics or adults. Two

recent series from the Mayo Clinic (USA) and the Institute Jacques-Cartier (Massey, France) had patient populations with median ages of 19 years and 34 years [139, 140]. There is not a reliable predictor of right heart failure post repair. In the Mayo clinic series, 24% of patients had a bidirectional cavopulmonary anastomosis or "one and half" ventricular repair. Also, 13% had an early re-operation for re-repair or valve replacement.

A concurrent anti-arrhythmia procedure, such as the Maze procedure, is frequently performed. In addition, the RV function might be inadequate post-repair and need support with milrinone and epinephrine. The aim is to minimize PVR and support systemic blood pressure. Conversion to spontaneous ventilation and early extubation is desirable. A relatively fast sinus rhythm appropriate for the age and judicious volume administration is critical. Good communication between the operative and ICU team with a goal for early spontaneous ventilation is vital. Chapter 28 contains an extensive discussion of Ebstein's anomaly and surgical approaches.

Noncardiac surgery

Ebstein's anomaly is high risk and merits referral to a cardiac reference center for management. Ideally, for elective procedures, a consultation with the multidisciplinary ACHD team and, in emergent cases, contact with the ACHD cardiology team and a congenital cardiac anesthesiologist.

A quarter of the patients had a bidirectional cavopulmonary (Glenn) shunt in the Mayo series [139]. The SVC anastomosed to the confluence of the left and right PAs. Care should be taken when placing central lines in these patients, as trauma may occur with the introducer, the wire, or the line itself, and a non-congenital cardiac anesthesiologist may miss this nuance and not appreciate that the line will transduce PA pressures.

As with TOF and failing hypokinetic RVs, patients with Fontan or total cavopulmonary connection will benefit from spontaneous ventilation techniques where possible. If positive pressure ventilation is indicated, it should be at a volume close to FRC. The RV might need support with milrinone, epinephrine or dobutamine, or a combination. For patients that have high right atrial pressures or cavopulmonary pressure, the head-down position can exacerbate it. MAP may have to be supported to ensure an adequate cerebral perfusion pressure.

Reversal of left to right shunt can occur even in the presence of device closure of an ASD. Many anesthetic agents, both intravenous and inhalational, are vasodilators that, in conjunction with positive pressure ventilation and insufflation of air or CO_2 into a body cavity, can raise intrathoracic pressure and PVR consequence, cause shunt reversal.

Single-ventricle anatomy/Fontan physiology

In an adult practice, patients with Fontan and Glenn shunt with single-ventricle physiology have been, for the most part, patients with tricuspid atresia, pulmonary atresia, and double inlet left ventricle, with morphological LVs as their systemic ventricles. However, increasingly, cardiac anesthesiologists see adults with hypoplastic left heart syndrome (HLHS) and systemic RVs. Fontan and Baudet first described the surgical correction of tricuspid atresia in 1971 [141]. There have been subsequent modifications to the procedure, all of which are present in adults followed in ACHD programs (see Figure 20.13) [142]. Most ACHD programs converted to either the lateral tunnel or the total cavopulmonary connection in the mid-1990s. Patients with a Fontan circulation will present for various interventions, including conversion of an RA to PA Fontan to a cavopulmonary connection, cardioversion, epicardial pacemakers, mapping, and ablation, and, in some cases, transplant.

The Australian New Zealand Fontan Registry has reported 413/1428 (29%) survivors of the Fontan procedure that underwent a late cardiothoracic reintervention (median 4.2 years, 30 days to 33 years) post-Fontan [143]. Excluding transplants and extracardiac Fontan conversions (ECFC), the proportion of patients with a dominant LV was consistent at 58% in both the late reintervention group and the no late intervention

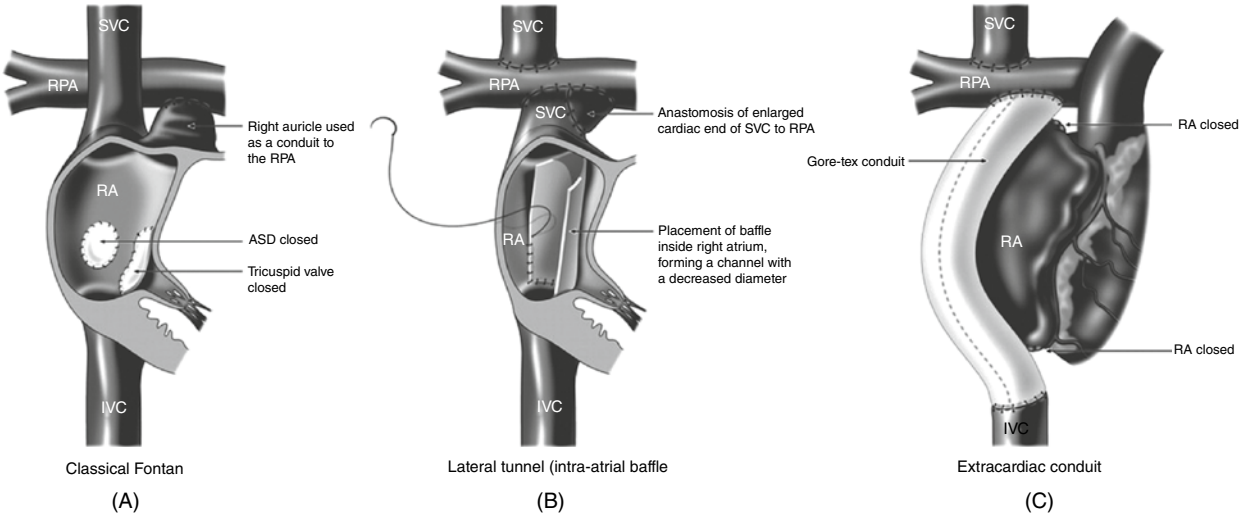


Figure 20.13 Various techniques of the Fontan procedure. (A) Atriopulmonary connection; (B) Lateral tunnel total cavopulmonary connection (TCPC); (C) Extracardiac conduit TCPC. Abbreviations: IVC, inferior vena cava; RA, right atrium; RPA, right pulmonary artery; and SVC, superior vena cava. (Source: d'Udekem et al. [142]. Reproduced with permission from Wolters Kluwer Health, Inc).

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Table 20.6 Late reinterventions excluding transplantation and conversion

	Overall, n (%) or median (IQR) *N* = 1428	No late interventions, n (%) median (IQR) *N* = 1034	Late interventions, n (%) median (IQR) *N* = 394	P – value
Dominant LV	832 (58)	602 (58)	230 (58)	0.958
Fontan type				
Atriopulmonary	218 (15)	116 (11)	102 (26)	<0.001
Lateral tunnel	277 (19)	179 (17)	98 (25)	<0.001
ECC	926 (65)	735 (71)	191 (48)	<0.001
Fenestration	523 (37)	340 (24)	183 (46)	<0.001

Abbreviations: IQR, interquartile range; LV, left ventricle; ECC, extracardiac conduit
Source: Adapted from Daley et al. [143].

group. The prevalence of the atriopulmonary Fontan is diminishing and at the time of publication was 15% (see Table 20.6). Forty-nine patients underwent Fontan conversion to ECFC at a median time of 18 years (range 5–29 years), and 31 patients underwent a heart transplant post-Fontan with a median time of 8 years (range 3 months–33 years)

Catheter-based interventions occurred in 220/413 (53%), of which fenestration closure was the most common (32%) median age 1.7 years (1 month–23 years) followed by catheter-based ablation of arrhythmia (13%) median age 20 years (3–31 years). Late re-operations occurred in 209 patients with pacemaker-related procedures occurring in 176 patients at a median age of 8.2 years (3.5–18 years). The remaining surgical interventions were in a pediatric age group with median ages less than 8 years and ranged into the late adolescent age. All late interventions described are markers for increased mortality [143].

The Mayo Clinic published their admissions experience of Fontan patients 18+ years over 25 years 1990–2015. There were 853 hospital admissions in 367 patients median age 31y +/− 7 years with a Fontan circulation, of which 259 (71%) had an atriopulmonary Fontan. Most of the admissions were arrhythmia-related 282 (33%), management, cardioversion, mapping, ablation, or heart failure-related 169 (20%). A minority had either cardiac 133 (16%) or noncardiac surgery 51 (9%)[144] (see Table 20.7).

Table 20.7 Procedures and outcomes of inpatient Fontan patients

	N	LOS (d)	In-hospital mortality
Fontan conversion/ revision	78 (9%)	6 (4–9)	10 (13%)
Valve replacement/ repair	41 (7%)	5 (4–8)	5 (12%)
Epicardial pacemakers/ defibrillators[a]	14 (2%)	3 (2–5)	0
Non cardiac procedures requiring GA	51 (9%)	3 (2–6)	1 (2%)

[a] Include surgical lead/generator implantation or revision.
Abbreviations: LOS, length of stay; d, days; GA, general anesthesia
Source: Adapted from Egbe et al. [144]

Most anesthetic encounters will be for nonsurgical interventions. Still, there will be cardiac and noncardiac surgical care in adults, rarely for a Fontan conversion/revision &/or transplant (see Figures 20.14 and 20.15). The physiological considerations are the same for the encounters but increasing complexity when the procedure conflicts with the physiological goals. A standard same-day procedure frequently will require in-hospital postoperative admission.

Arrhythmia, electrophysiology, and diagnostic procedures

The is no direct vascular access to the heart in lateral tunnel Fontan or a total cavopulmonary connection challenging the anesthesiologists. Challenges exist for cardioversion, mapping, and atrial ablation arrhythmias. Cardioversion of the adult Fontan can be safe but requires planning [145].

Arrhythmia is a significant complication of the original Fontan conversion and often signals the beginning of failing Fontan circulation and subsequent decreases in quality of life. Medical management is usually ineffective at preventing arrhythmia recurrence, and the required electrophysiological studies are complex and time-consuming but less so than a Fontan conversion. Early referral for radiofrequency ablation or Fontan conversion is essential as a longer duration of arrhythmia is a risk factor for arrhythmia recurrence [146].

The goals in an electrophysiology intervention are to maintain spontaneous ventilation without inadvertently raising the $PaCO_2$ of the patient and adversely affecting the PVR and diminishing trans pulmonary blood flow. Transconduit mapping is possible with radiofrequency transeptal techniques. Fenestrations to the atrium from the lateral tunnel or the conduit of the cavopulmonary connection are a restricted window for the electrophysiologist, akin to painting an interior room of a house through a small window in an exterior wall while standing on a ladder. Remote magnetic navigation uses retrograde access; however, it is a costly setup and not widely available [147]. The procedures are lengthy for both the anesthesiologist and the patient. The patient must not be too sedated so that the electrophysiologist physician can map the arrhythmia and yet should be comfortable to remain still for several hours. Conversion to a spontaneously breathing technique with a supraglottic airway is an option. Recovery in a monitored environment is essential. A checklist for cardioversion in the Fontan patient is presented in Table 20.8.

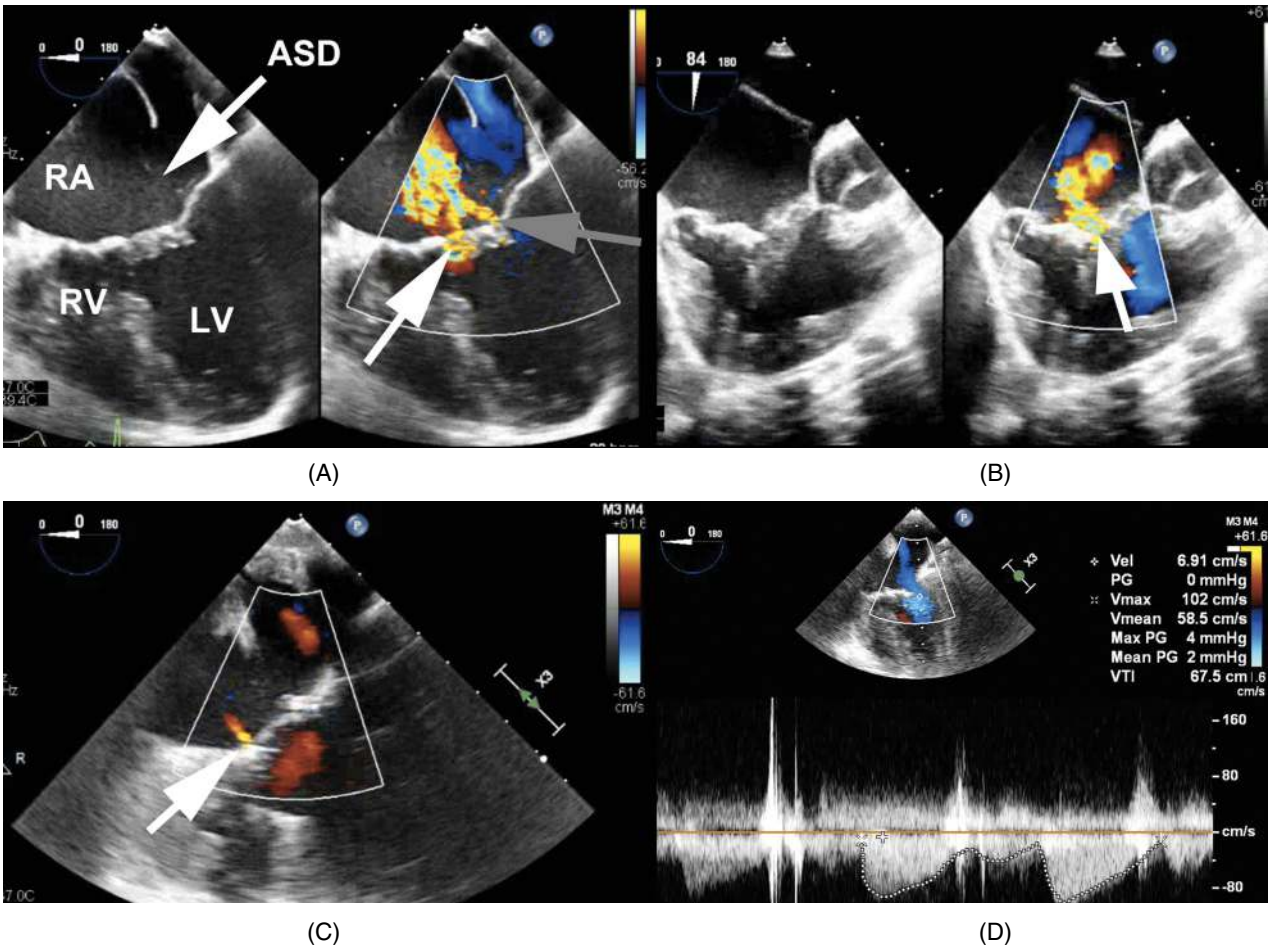


Figure 20.14 TEE images of a Fontan patient with unbalanced CAVC Rastelli type 3 (hypoplastic RV) with an unrestrictive primum ASD (white arrow) and severe AVV regurgitation who underwent AVV repair; (A) Mid esophageal four-chamber view showing a complex AVV regurgitation jet with two different components, a bigger jet along commissures between the superior bridging, inferior bridging, and right lateral leaflets (white arrow) and a smaller regurgitant jet between the superior bridging and inferior bridging leaflets (gray arrow); (B) Mid esophageal two-chamber view displaying the complex AVV regurgitation (arrow); (C) Mid esophageal four-chamber view exhibiting trivial regurgitation post AVV repair; (D) Pulse wave Doppler at the same window without evidence of AVV stenoses with a mean gradient of 2 mmHg. Abbreviations: RA, right atrium; RV, right ventricle; ASD, atrial septal defect; LV, left ventricle; AVV, atrioventricular valve.

Fontan conversion

Several centers have published successful case series of Fontan conversion with concomitant arrhythmia surgery. The median age varies from late teens to early adulthood [148, 149]. The goal is to improve hemodynamic and loss of energy in the blood flowing into the PA, lessen the risk of thrombo-embolic events, and prevent atrial dilatation and subsequent arrhythmias. A recent publication of a multicenter study of 522 adult patients found atrial arrhythmias were substantially lower with a total cavopulmonary connection Fontan compared to atrio-pulmonary Fontan. The median duration of follow-up was 11.6 years. Forty of the 522 patients underwent conversion from an atrio-pulmonary Fontan [25] or a lateral tunnel [12], and three had the transformation of an intracardiac to an extracardiac circulation [150].

Fontan conversions are a high-risk surgical procedure due to the complex anatomy and multiple previous operations. The anesthetic and ICU goals are to use agents and ventilation strategies that minimize PVR. Intraoperative or early ICU extubation is the goal. Conversion to an ECFC may improve quality of life and lessen the arrhythmia burden, but it is uncertain if this will translate to improved mortality. An extensive follow-up cohort in Boston found no difference in long-term survival between RA to PA connection Fontan and total cavopulmonary connections [150]. An analysis of 683 adult survivors in the Australian New Zealand Fontan registry found survival at 30 years of age was 86% for patients with atriopulmonary Fontan versus 93% for patients with an extracardiac Fontan. The differences in survival may be due to an era effect rather than technique, and the most common mode of death was cardiac failure. Only 9/683 had a conversion, and it is uncertain if conversion at an adult will translate to improved survival [151].

Noncardiac surgery and the patient with a Glenn Shunt, Hemi-Fontan, or Fontan

Reference centers cannot meet the demands of obstetrical and noncardiac of all patients with complex CHD. However, those with single ventricles, Glenn with a "One and a Half"

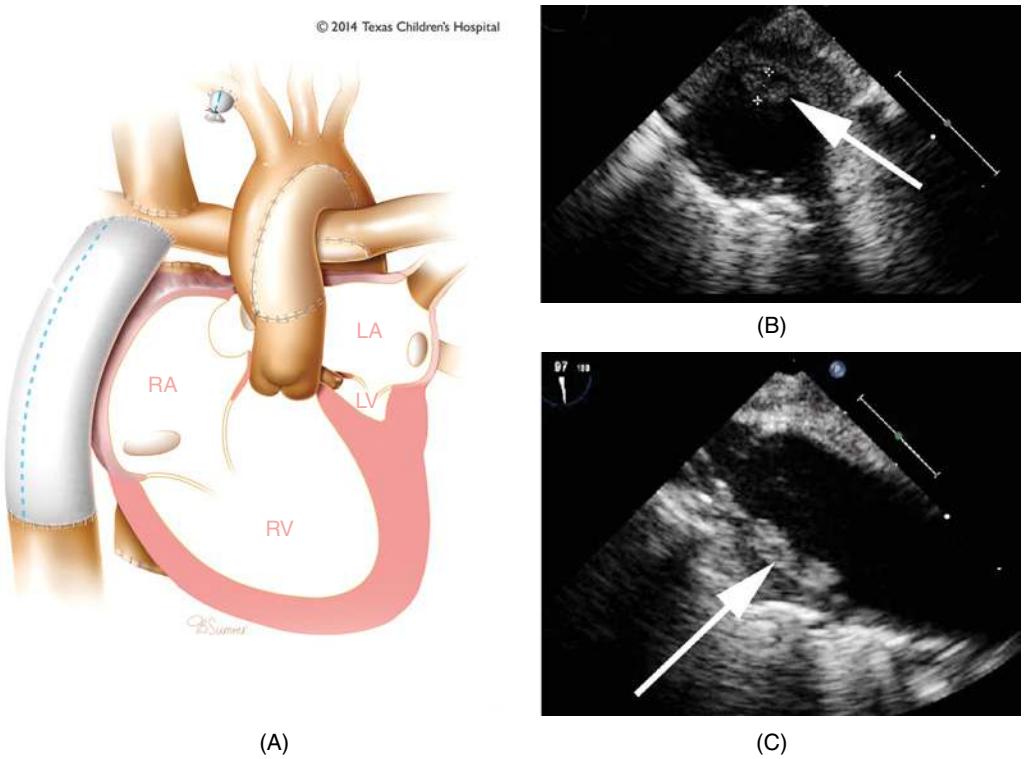


Figure 20.15 (A) Illustration of the Fontan circulation in HLHS; (B) TEE short axis view showing an immobile echo density visualized in the posterior wall of the Fontan baffle (white arrow); (C) TEE long axis view displaying another immobile echo density in the anterior medial wall of the Fontan baffle (white arrow). Abbreviations: RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; HLHS, hypoplastic left heart syndrome. Source: Reproduced with permission from Texas Children's Hospital.

Table 20.8 Check list for cardioversion in the fontan patient

1. Pacing pads on A-P	☐
2. Central location in the hospital	☐
3. Notification of an experienced colleague to call for assistance.	☐
4. Resuscitation drugs, epinephrine, calcium, immediately available	☐
5. Large gauge iv	☐
6. Avoid positive pressure ventilation, pre-oxygenate prior to the electrical stimulus.	☐
7. "Light" use of hypnotics and patience in waiting for the circulation and loss of consciousness.	☐
8. A plan for treating bradyarrhythmia post conversion.	☐

ventricle repair, and those with Fontan palliation must be reviewed by a multidisciplinary team or referred for management. Patient preference is a significant driver of choosing to go to a reference center rather than stay in the community. The Mayo Clinic group analyzed 538 noncardiac procedures in 154 Fontan patients (mean age, 30 years) from 1990 to 2015. A broad range of procedures and anesthetics were included, except for neurosurgical/intracranial. Fifty-one (9%) of the patients required general anesthesia. Overall, hypoxia was the most common intraoperative and postoperative complication, followed by hypotension and arrhythmia [152].

Multidisciplinary team consultation assessing the procedure's impact on single ventricle physiology patients must be evaluated by an interdisciplinary team. For example, a college student living away from home, with good systemic ventricular function and free of arrhythmias, needing dental extractions can be managed in a regional hospital setting with clear lines of referral to the reference center if required. Alternatively, a patient with decreased single ventricular function needing an urgent intrabdominal procedure will need care in a tertiary center. Neurosurgical patients (e.g., spinal instrumentation) merit both a cardiac anesthesiologist and a subspecialty neurosurgical anesthesiologist.

A classic Glenn shunt is an SVC directly anastomosed to the right PA. A bi-directional Glenn shunt is the SVC anastomosed to the confluence of the left and right PAs. When placing central lines in patients with Glenn shunts; trauma may occur with the introducer, the wire, or the line itself. Fontan patients have no "pump" for systemic venous return to get to the LA. For successful management, they must have adequate right-sided filling pressures, low PVR, unobstructed pulmonary vein inflow to the LA, AV synchrony, a competent systemic AV valve with laminar inflow, no outflow tract obstruction, and reduced afterload for the systemic ventricle. Patients may have had a fenestration from the Fontan connection to the systemic or common atrium, and precautions for venous emboli to the systemic circulation will be needed. Conversion to the spontaneous breathing mode of ventilation and early extubation are the objectives at the end of surgery.

KEY POINTS: SINGLE-VENTRICLE/FONTAN ANATOMY

- Early Fontan palliations due to right heart failure and arrhythmias necessitate conversion to lateral tunnel or extracardiac connections in some adults.
- Treatment of HLHS with the Fontan operation since the 1980s has created a growing population of young adults with failure of the systemic RV.
- Avoidance of prolonged positive pressure ventilation and hypovolemia are important anesthetic considerations.
- Arrhythmia procedures, mapping/ablation, pacemakers, and cardioversion are frequent in the adult Fontan and require careful planning and backup during emergencies.

Heart failure in ACHD

End-stage heart disease (ESHD) is particularly prevalent in single ventricle physiology (e.g., Fontan), systemic RV (d-TGA after Mustard/Senning or L-TGA), severe PAH (e.g., Eisenmenger-Syndrome), and severe valvular heart disease (e.g., post-CAVC repair) [153]. Traditionally, the treatment of ESHD is an orthotropic heart transplant. Patients with ACHD listed for transplant spend more time in the waiting list due to antibody sensitization to red cell antigens, and complex anatomy requiring specific graft allocation (e.g., need for extensive PA or aortic reconstruction). Formerly rare, patients with ACHD are now increasingly supported with VAD. Earlier use of VAD before the development of multiorgan failure increases survival in the ACHD population [154]. Only 5% of the adult heart transplant population are patients with ACHD [155]. Failing Fontan patients due to the high incidence of liver and renal failure need to be listed early even though multi-solid organ transplantation has been performed successfully [156]. Patients with Fontan circulation, complex anatomy, and PAH have a higher surgical risk [157].

Noncardiac surgery in the adult with CHD

Congenital cardiac anesthesiologists and intensivists have an exceptional understanding of ACHD patient's unique physiology. They must play a leadership role, providing care directly or advising colleagues in the community how best to provide care for these patients and when it is necessary to transfer care. This expertise is not limited to the operating room but should also be available in preoperative optimization and planning, postoperative monitoring, and pain management [158–161]. There are patient factors that will bias toward management at the tertiary referral center (see Table 20.9). Should an event occur in an ACHD center, there is much more latitude in the deployment of staff to assist in a hemodynamic or volume resuscitation.

Laparoscopic and video-assisted is becoming the standard for general surgical, gynecological, and urological operations.

Table 20.9 Red flags for referral to a reference center

Cyanosis or a deterioration in oxygenation from baseline	☐
Single ventricle	☐
Glenn or Fontan palliations	☐
Pulmonary hypertension	☐
New onset of arrhythmia or difficult rate control in an established atrial arrhythmia	☐
Systemic hypotension in relation to the patient's baseline	☐
Systemic ventricle dysfunction	☐

For example, thoracic surgery utilizes air insufflation, as the chest wall is rigid, and CO_2 is not needed. PVR will rise if the lung is atelectatic during one-lung ventilation but not from absorption insufflated CO_2. Similarly, in robotic surgery, insufflation of air with mechanical tenting of the abdominal wall is used. Insufflation of CO_2 might affect the PVR, but minimally invasive approaches improve postoperative recovery. Patient positioning (e.g., prone, lateral, Trendelenburg, or reverse Trendelenburg) may exacerbate or alleviate this conflict. The team should have a clear plan for conversion to an open procedure. Although challenging for the anesthesiologist, the patient benefits from a closed procedure and avoids the complications of a large incision. Additional benefits include less intravenous opioid use and will be less likely to have chest splinting, atelectasis, and elevated $PaCO_2$.

Head and neck and upper airway surgery with either a controlled airway or suspension laryngoscopies for glottic and subglottic complications of prolonged intubation are not unusual cases in patients with ACHD. It is not the choice of anesthesia agents but the maintenance of physiologic goals that is the challenge. Spontaneous ventilation in a PVR dependent patient will eliminate the concerns of positive pressure ventilation impeding blood flow from the vena cavae and right to the LA. Laryngoscopy and bronchoscopy with jet ventilation are challenging procedures in single ventricle, PAH, and shunt physiology patients.

Major spine surgery in the prone position is demanding in ordinary circumstances and, more so in patients with ACHD. Retrospective single-center reviews of complex CHD adolescent patients highlight multidisciplinary team planning and perioperative management [162, 163]. Pulmonary function evaluation preoperatively is indicated [164]. In larger, multilevel cases, considerable blood loss can occur, and blood conservation strategies are required. In addition, the technical challenges of spinal instrumentation in patients with complex cardiac disease merit a multidisciplinary anesthesia team (e.g., cardiac and neuro anesthesia). The one teaching hospital death in a long series of Eisenmenger syndrome adults for noncardiac surgery was an inpatient who had come in for spinal instrumentation [165].

Many patients will be receiving ongoing monitoring and support in an established ACHD center; however, frequently, a surgeon will be the patient's first contact with a specialist physician in several years of having been lost to follow-up. Community anesthesiologists and surgeons are in a unique situation to identify a patient at risk and, in addition to pre-, intra-, and postoperative care, reconnect them to an ACHD team for subsequent care. The consultant

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ACHD anesthesiologist can facilitate the surgery and act as a resource for the noncardiac anesthesiologist [158].

Conclusions

The survivor ACHD patient of a pediatric intervention or presenting for the first time as an adult may need anesthesia care for diagnostic, therapeutic, noncardiac surgery, cardiac surgery, and ICU management. The skills, knowledge, and career experience of a congenital cardiac anesthesiologist are vital to the care of this unique patient population. In addition, as the proportion of adults living with CHD continues to dominate the congenital cardiac population increasing resources at reference centers and the ability to support patients in the community setting with outreach and referral lines is essential to the well-being of these patient populations.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

10 Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation [Internet] 2019 [cited 2021 May 16];139(14). https://www.ahajournals.org/doi/10.1161/CIR.0000000000000603. AHA/ACC is a detailed, evidence-based practice guideline for the Management of Adults with Congenital Heart Disease. It discussed the role of the cardiac anesthesiologist in the perioperative period.

33 Favoccia C, Constantine AH, Wort SJ, Dimopoulos K. Eisenmenger syndrome and other types of pulmonary arterial hypertension related to adult congenital heart disease. Exp Rev Cardiovasc Ther 2019;17(6). This paper is an overview of Eisenmenger syndrome and other types of pulmonary arterial hypertension related to ACHD. In addition, the authors described the medical management in tertiary centers, emphasizing comorbidities and complications.

52 Gordon-Walker TT, Bove K, Veldtman G. Fontan-associated liver disease: a review. J Cardiol 2019;74(3). This comprehensive review article tackles all the liver disorders secondary to Fontan physiology. It is well written and has didactic illustrations.

64 Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39(34):3165–241. https://doi.org/10.1093/eurheartj/ehy340. The European Society of Cardiology (ESC) summarizes and evaluates all available evidence of acquired and congenital cardiovascular diseases during pregnancy. In addition, the ACHD section analyses the implication of each congenital lesion individually through pregnancy.

68 Canobbio MM, Warnes CA, Aboulhosn J, et al. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2017;135(8):e50–e87. https://doi.org/10.1161/CIR.0000000000000458. The scientific statement by the AHA addresses the management of preconception counseling, evaluation of maternal-fetal risk and pregnancy referral, and treatment.

92 Arendt KW, Lindley KJ. Obstetric anesthesia management of the patient with cardiac disease. Int J Obstet Anesth 2019;37. https://doi.org/10.1016/j.ijoa.2018.09.011. The authors published a review article on the obstetric anesthesia management of the patient with acquired and congenital heart disease. In addition, didactic tables present the pregnancy effects and anesthetic goals for each cardiovascular disease in pregnancy.

121 Mongeon F-P, ben Ali W, Khairy P, et al. Pulmonary valve replacement for pulmonary regurgitation in adults with tetralogy of Fallot: a meta-analysis – a report for the Writing Committee of the 2019 Update of the Canadian Cardiovascular Society Guidelines for the Management of Adults With Congenital Heart Disease. Can J Cardiol 2019;35(12). The consensus paper highlights the evolution of Tetralogy of Fallot repair over time and how different eras have varying outcomes for the adult patients. It also highlights the way forward for the ACHD community is participation is international registries examine disease specific lesions.

125 Montanaro C, Merola A, Kempny A, et al. The outcome of adults born with pulmonary atresia: high morbidity and mortality irrespective of repair. Int J Cardiol 2019;280. This article demonstrates the complexity and heterogeneity of Pulmonary atresia. Anaesthetic management must be tailored to the individual patient's anatomy.

143 Daley M, du Plessis K, Zannino D, et al. Reintervention and survival in 1428 patients in the Australian and New Zealand Fontan Registry. Heart 2020;106(10). This article highlights the evolution of the Fontan procedure since introduction in 1971 and the nuances in managing the mature Fontan patients.

157 Bryant III R, Morales D. Overview of adult congenital heart transplants. Ann Cardiothorac Surg 2018;7(1). The authors present a review article with the current challenges of the ACHD end-stage population. They describe the scope of ACHD transplantation, mechanisms of ventricular dysfunction in ACHD, and the indications and potential contraindications for transplant.

CHAPTER 21

Hemodynamic Management

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Introduction: Hemodynamic management following congenital heart disease surgery: a goal-directed approach

Guidelines delineate limits within which decisions can be made regarding the management of specific clinical problems to improve outcome. A more prescriptive approach often takes the form of "goal-directed" therapy, and the key to the success of any goal-directed therapy is the selection of the specific goal [1]. A meta-analysis of randomized studies of adult patients [2] in various postoperative settings demonstrated a strong relationship between the duration and magnitude of oxygen debt and outcomes in high-risk patients. There was a significant improvement in survival when pulmonary artery catheter goal-directed therapy was administered early or prophylactically (within 12–24-hour postsurgery or before organ failure occurred) to increase the cardiac index and oxygen delivery (DO_2). The aim of this goal-directed therapy was intervention before hemodynamic compromise or critical organ system compromise occurred, because no amount of extra oxygen would rescue irreversible oxygen debt, organ failure, or cell death. Maintaining adequate tissue oxygenation, which is accomplished by optimizing oxygen transport balance, i.e., maintaining systemic DO_2 and minimizing oxygen consumption (VO_2), should prevent oxygen debt and improve outcome. In complex and high-risk situations, such as following congenital heart disease (CHD) surgery, the use of evidence-based clinical guidelines and associated goal-directed therapy has the potential to improve clinical outcomes. Preventing oxygen debt is probably the ultimate goal when treating children who have undergone surgery for CHD.

The VO_2/DO_2 balance following CHD surgery

In 1995, Wernovsky et al. published a prospective study comparing deep hypothermic circulatory arrest and continuous low-flow cardiopulmonary bypass in neonates undergoing the arterial switch operation [3]. The perfusion strategy assignment was not associated with the postoperative hemodynamics. However, the hemodynamic measurements performed on 122 patients revealed that during the first

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postoperative night, the cardiac index decreased by average 30% in almost one quarter of patients. Consequently, much effort has been put into augmenting CO, and the PRIMACORP study [4] demonstrating the benefit of the preventive use of a potent vasodilator to increase CO was a milestone in the field. Later on, using continuous respiratory mass spectroscopy to measure oxygen consumption, arterial, superior vena cava (SVC), and pulmonary venous saturations to measure DO_2 in 14 neonates undergoing the Norwood procedure, Li et al. [5] reported low CO and systemic DO_2 during the first 12 postoperative hours; VO_2 was high postoperatively and progressively decreased over the first 24 hours. The decrease in VO_2 during the first 24 h was the main contributor to improving the VO_2/DO_2 balance, pointing to the rationality of postoperative strategies to decrease VO_2 in critical cases.

A pathologic imbalance between VO_2 and DO_2 is thought to be the mechanism underlying anaerobic metabolism, multisystem organ failure, and death. The oxygen extraction rate (OER), calculated as

$$\mathrm{OER} = \mathrm{VO_2} / \mathrm{DO_2} \tag{21.1}$$

might best reflect the oxygen consumption/delivery balance. The normal ratio of four to five times the amount of DO_2 to VO_2 suggests considerable reserve, and decreasing this factor (or increasing the OER) reflects less cardiovascular reserve. At high DO_2, VO_2 remains both stable and oxygen supply independent. During periods of reduced DO_2, aerobic metabolism is maintained initially through increased oxygen extraction by the tissues. Through this mechanism, VO_2 remains independent of DO_2 until a critical OER is reached. At that point, which is generally thought to correspond to an OER between 0.5 and 0.6, [6], VO_2 becomes oxygen supply-dependent and drops linearly to zero if DO_2 decreases further. An OER above 0.5 has a positive predictive value of 74% for postoperative death in infants following CHD surgery [7]. The inflection point between the two slopes of the DO_2 curve indicates the critical level of DO_2. An illustration of these relationships is shown in Figure 21.1.

The relationship is altered further when VO_2 increases. When VO_2 increases, which is common in the postoperative period, the critical DO_2 also increases, as shown in Figure 21.1,

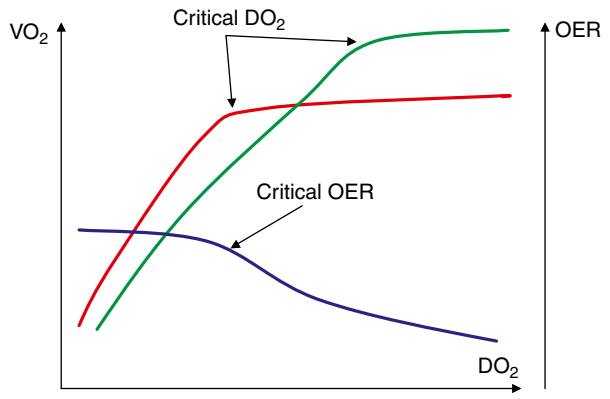


Figure 21.1 Pathophysiological changes in the relationship between oxygen consumption (VO_2) and oxygen delivery (DO_2). (Source: Squara [8]. Reproduced with permission of Springer Nature.)

meaning that a VO_2/DO_2 imbalance occurs at higher DO_2 levels. Therefore, it follows that one of the postoperative strategies is to increase DO_2 to delay the point at which a VO_2/DO_2 imbalance may occur.

The Fick equation states that

$$\mathrm{CO} = \mathrm{VO_2} / \left(\mathrm{CaO_2} - \mathrm{CvO_2}\right) \tag{21.2}$$

where CO is the cardiac output, and CaO_2 and CvO_2 are the oxygen content of arterial and venous blood, respectively. At steady state, on the basis of the law of mass conservation, oxygen consumption and delivery must be equal.

$$\mathrm{VO_2} = \mathrm{DO_2} \tag{21.3}$$

In the setting of CHD, DO_2 is a resultant of several factors.

In the absence of intracardiac shunting, CO is equivalent to the systemic output (Q_S) and the pulmonary output (Q_P).

$$\mathrm{CO} = \mathrm{Q_S} = \mathrm{Q_P} \tag{21.4}$$

and systemic DO_2 is a linear function of CO and CaO_2:

$$\mathrm{DO_2} = \mathrm{CO} \times \mathrm{CaO_2} \tag{21.5}$$

These indexes change slightly in patients with univentricular physiology, as described below [9, 10].

Following the first stage of the Norwood palliation, the systemic and pulmonary circulations become parallel, and the single ventricle assumes both the systemic and the pulmonary output:

$$\mathrm{CO} = \mathrm{Q_S} + \mathrm{Q_P}. \tag{21.6}$$

If making the assumption that the pulmonary oxygen uptake equals VO_2, then one can write separately:

$$\mathrm{Q_S} = \frac{\mathrm{VO_2}}{\left(\mathrm{CaO_2} - \mathrm{CvO_2}\right)} \tag{21.7}$$

and

$$\mathrm{Q_P} = \frac{\mathrm{VO_2}}{\left(\mathrm{CpvO_2} - \mathrm{CaO_2}\right)} \tag{21.8}$$

where $CpvO_2$ is the pulmonary venous blood oxygen content.

We can combine these equations as follows:

$$\mathrm{DO_2} = \frac{\mathrm{CO} \times \mathrm{CpvO_2}}{\left(1 + \mathrm{Q_P}/\mathrm{Q_S}\right) - 2/\left(\mathrm{Q_P}/\mathrm{Q_S}\right)} \tag{21.9}$$

which shows that DO_2 is a complex function of CO, pulmonary venous oxygen content, VO_2 and Q_P/Q_S ratio [9].

Following the bidirectional Glenn anastomosis, the blood that normally drains into the right atrium (RA) from the SVC is redirected to the pulmonary artery, and forms a combined upper systemic and pulmonary circulation, which is in parallel with the lower systemic circulation. The overall CO is a sum of the upper and lower systemic output:

$$\mathrm{CO} = \mathrm{Q_{SVC}} + \mathrm{Q_{IVC}} \tag{21.10}$$

Since $Q_P = Q_{SVC}$, it results that

$$\mathrm{CO} = \mathrm{Q_P} + \mathrm{Q_{IVC}} \tag{21.11}$$

On the other hand,

$$VO_2 = k \times VO_2 + (1-k) \times VO_2 \quad (21.12)$$

states that the whole-body VO_2 is the sum of the upper body oxygen consumption ($k \times VO_2$) and that of the lower body [$(1 - k) \times VO_2$], where k is the fraction consumed by the upper body.

If making the assumption that oxygen uptake through the pulmonary circulation equals VO_2, then one can write separately:

$$Q_{SVC} = \frac{(VO_2 \times k) = Q_P}{(CpvO_2 - CaO_2)} \quad (21.13)$$

and

$$Q_{IVC} = \frac{(VO_2 \times (1-k))}{(CaO_2 - CvO_2)} \quad (21.14)$$

We can combine these equations as follows:

$$DO_2 = CO \times CpvO_2 - (1 + Q_{SVC} / Q_{IVC}) \times \frac{((1-k) \times VO_2)}{(Q_{SVC} / Q_{IVC})} \quad (21.15)$$

which shows that DO_2 is a complex function of cardiac output, pulmonary venous blood oxygen content, lower body oxygen consumption and Q_{SVC}/ Q_{IVC} ratio [10].

To resume, albeit in a majority of patients, the postoperative DO_2 is a linear function of CO and CaO_2, there are cases where DO_2 is a complex function of several other factors. Thus, if the goal is to balance postoperative VO_2/DO_2, then focusing on CO alone is probably not the right strategy.

Changes in systemic oxygen balance have been well-documented in adults and children undergoing surgery with cardiopulmonary bypass (CPB) [5, 11, 12], with VO_2 increasing and DO_2 decreasing within the first 8–12 hours postoperatively. Fortunately, increases in VO_2 are usually closely paralleled by changes in DO_2, and OER varies little in patients with stable cardiac function postoperatively [11].

Mechanisms underlying increases in VO_2 following CHD surgery

Evidence suggests that 50% of the postoperative increase in VO_2 in adults is due to inflammatory responses, and that variations in VO_2 are strongly correlated with the circulating levels of endotoxin, tumor necrosis factor and interleukin-6 concentrations [12].

Alterations in pulmonary function following cardiac surgery result in increased work of spontaneous breathing, which may require the redistribution of up to 15–20% of CO away from other organs [13]. Additionally, even when sedation and neuromuscular blockade was maintained to obviate the confounding effects of spontaneous ventilation, movements, agitation, and pain on VO_2, Li et al. [11] demonstrated a mean 14.7% increase in VO_2 within 4 hours of CHD surgery. The main determinants of this increase were a low age and an increase in central temperature, with an approximate 11% rise in VO_2 per degree of increase in central temperature following hypothermic CPB [11].

Box 21.1 Factors responsible for a postoperative increase in oxygen consumption

- Systemic inflammatory response
- Fever
- Spontaneous breathing
- Consciousness, pain anxiety
- Catecholamines: endogenous and exogenous
- Enteral nutrition

Source: Adapted from Bronicki et al. [18].

The increase in VO_2 is more substantial in children than in adults for several additional reasons. First, young infants have greater resting VO_2 and experience greater inflammatory responses when compared with older patients with CPB. Deep hypothermia is more frequently used during pediatric cardiac operations, and active rewarming restores only 65% of the heat loss, with muscles and subcutaneous fat remaining hypothermic at the end of CPB [14]. Strong biochemical and hormonal stress responses occur in young children following cardiac surgery, further increasing VO_2 [15].

Finally, treatments used in an effort to improve CO may have complex or even adverse effects. Catecholamines augment cardiac contractility and DO_2 and also stimulate VO_2 through their effect on myocardial work and metabolic rate [16]. If the increase in DO_2 is greater than the increase in VO_2, then catecholamines will improve overall balance of tissue oxygenation. In neonates, however, catecholamines have additional thermogenic actions through their effect on brown adipose tissue [17], resulting in an exaggerated increase in VO_2 (Box 21.1).

Mechanisms underlying reduced DO_2 following CHD surgery

Equation (21.5) shows that DO_2 decreases are a result of a reduction in CaO_2, or a reduction in CO. Equation (21.5) can be rewritten as:

$$DO_2 = CO \times (\text{hemoglobin}(g/dL) \times 1.34 \times SaO_2 + PaO_2 \times 0.003) \quad (21.16)$$

The main determinants of CaO_2 are the hemoglobin concentration and SaO_2. The ideal hemoglobin concentration and management of perioperative transfusions largely depend on age and on the underlying CHD and will not be discussed further. Postoperative bleeding is a major risk factor of low cardiac output syndrome (LCOS), through on the other hand, hypoxemia following cardiac surgery is multifactorial. CPB and reperfusion result in an intense generalized inflammatory reaction and diffuse endothelial damage accompanied by an increased vascular permeability, both of which induce pulmonary injury. Alveolar and interstitial edema, which may or may not be clinically apparent, reduce dynamic lung compliance and increase the ventilation/perfusion mismatch. A reduction in functional residual capacity (FRC) after anesthesia and thoracic surgery may result in worsening of hypoxia.

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However, the major driver of a low postoperative DO_2 is LCOS. LCOS is a common complication following CHD surgery in infants. Wernovsky et al. reported that 25% of neonates following the arterial switch operation showed a decline in cardiac index to <2 L/min/m^2, which typically occurred between 6 and 18 hours after surgery [3]. The prevalence of LCOS in other studies was even higher, reaching 40% [19, 20]. This fall in the cardiac index was associated with an increase in systemic vascular resistance (SVR) of approximately 25%, and an increase in pulmonary vascular resistance (PVR) of nearly 40% over baseline values [3]. These findings were confirmed experimentally, showing a 15% decrease in CO occurring 2–4 hours after CPB in piglets [21]. The decrease in CO was concomitant with a 19% increase in PVR and an equivalent increase in systemic arterial elastance, both reversed by the preventive use of milrinone and levosimendan (which are systemic and pulmonary vasodilators).

It appears that, by contrast with most of the adults, neonates and infants develop LCOS with high SVR and PVR following CPB. Under normal circumstances, increased afterload is accompanied by a compensatory increase in ventricular contractility to maintain the stroke volume, known as ventriculovascular coupling. During experimental post-cardiac surgery LCOS, it has been shown that there is a lack of compensatory increase in ventricular contractility [21], and that therapeutic interventions aiming at reducing afterload actually prevented a reduction in CO. Figure 21.2 shows ventricular pressure–volume loops while varying afterload, preload, and inotropy. It shows that an increased afterload results in a decrease in the stroke volume and an increase in the workload, and thus VO_2, of the ventricle. However, several myocardial stresses occur during cardiac surgery, including ischemia–reperfusion injury, inflammatory response, cardioplegia, and oxidative stress, and will invariably cause some degree of postoperative myocardial oxygen debt and dysfunction. Thus, an increase in the afterload creates a challenging situation, where the myocardium has to cope with an increased VO_2 while recovering from oxygen debt.

Evidence suggests that even patients undergoing atrial septal defect closure with short CPB and cross-clamping durations suffer from left ventricle (LV) systolic dysfunction, with a decrease in end-systolic elastance by 40% (Figure 21.3); this occurs independently of the type of cardioplegia and age [22]. Myocardial function is further impaired in patients undergoing complex repairs requiring ventriculostomies and large pericardial patches, in whom myocardial stunning is common. Myocardial dysfunction in neonates may be even more pronounced; neonates are known to have a relatively fixed stroke volume and their CO is known to be highly dependent on heart rate. They have diminished myocardial reserves to increase contractility, due to the immaturity of the neonatal myocardium: greater noncontractile component of myocardium, decreased norepinephrine stores, lower sarcoplasmic reticulum content, and high reliance on extracellular calcium regulation. In univentricular hearts, these reserves are marginal, and efforts to improve DO_2 by intropic agents, which increase the myocardial VO_2, are more likely to be associated with adverse effects.

CPB results in early dysfunction of the pulmonary endothelium and an increase in PVR [23]. Endothelial dysfunction is a consequence of the systemic inflammatory responses, alongside ischemic insult to the parenchyma itself, which occurs as a consequence of exclusive bronchial perfusion during bypass. Bronchial perfusion is further reduced in deeply cyanosed patients, or in those who have major aortopulmonary collaterals, in whom a significant backflow from the aorta to the branch pulmonary arteries via the pulmonary circulation is observed. Endothelial dysfunction is accompanied by sequestration of activated neutrophils within the pulmonary microcirculation, capillary leak and increased extravascular water levels, reduced surfactant function, atelectasis, and an increased pulmonary shunt. Additional postoperative factors, such as pain, hypoxia, hypercarbia, and acidosis, may cause an increase in PVR, particularly in neonates. Increased PVR can be particularly problematic in neonates, in whom PVR is already high, and in young infants with increased preoperative pulmonary blood flow. Right ventricular (RV) failure due to acute pulmonary hypertension (PHT) is often associated with LCOS and hypotension which, added to the increased

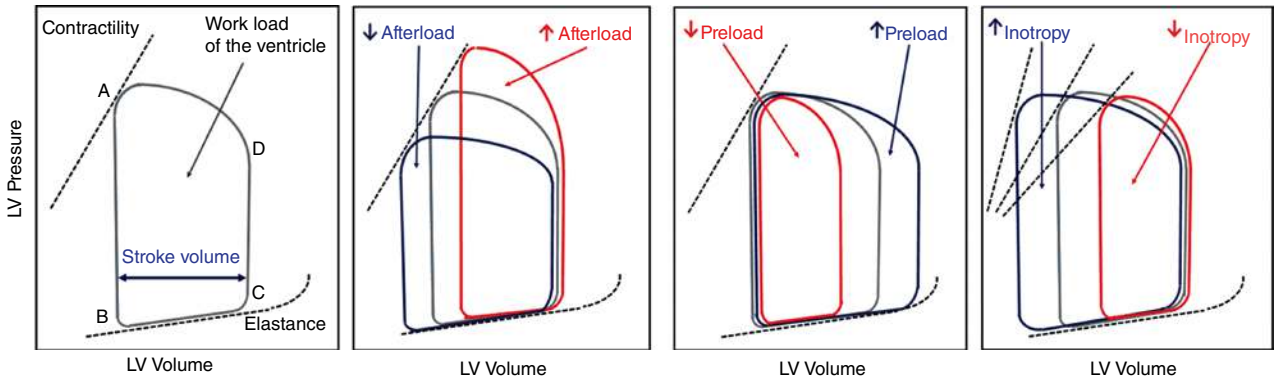


Figure 21.2 Ventricular pressure volume loops and effect of varying afterload, preload or inotropy on the stroke volume and work load. An increased afterload, as seen in post-CHD surgery in infants, results in a decrease in the stroke volume and an increase in the workload of the ventricle, a challenging postoperative situation. Decreasing the afterload results in an increased stroke volume and an equivalent work load of the ventricle. Both the increase in preload and inotropy result in an augmented stroke volume, with a concomitant increase, however, in the workload of the ventricle. It appears that, in the context of post-CHD surgery LCOS in infants, vasodilators increase the stroke volume without affecting myocardial oxygen demand, and represent, therefore, the most effective option. A: aortic valve closes, B: mitral valve opens, C: mitral valve closes, D: aortic valve opens.

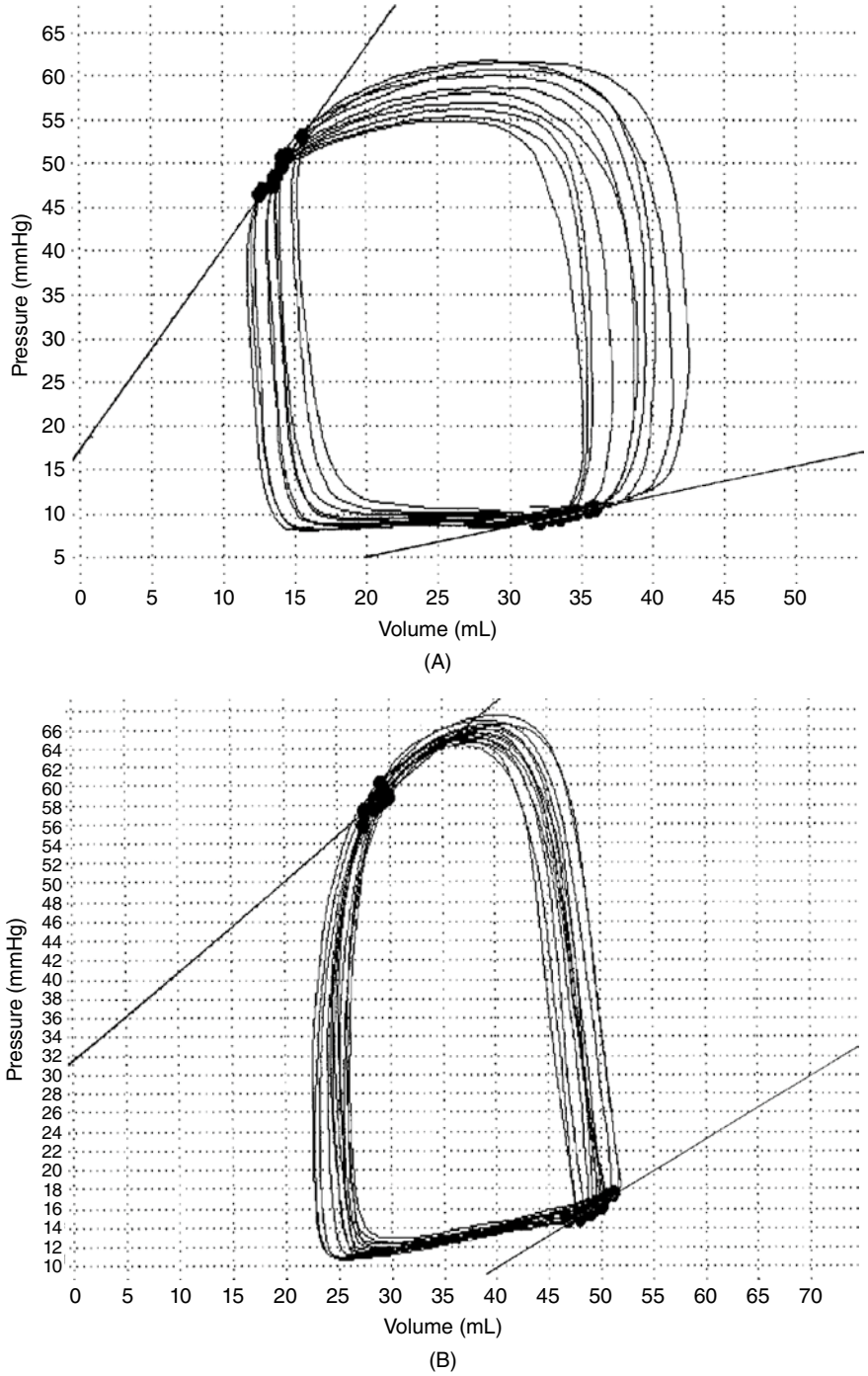


Figure 21.3 Left ventricular pressure–volume loops from infants and children undergoing closure of atrial septal defect with short bypass and cross-clamping durations. (A) Pre-bypass; (B) post-bypass (Source: Chaturvedi et al. [22]. Reproduced with permission of Elsevier.)

RV pressure, reduces the RV coronary perfusion pressure, and may further reduce RV contractility. Even transient pulmonary pressure overload may induce persistent RV failure.

Finally, LCOS may develop due to various reasons specific to the underlying CHD and to the surgical procedure. Coronary diastolic perfusion may be decreased following a systemic–pulmonary anastomosis as seen following the Norwood procedure, and results in dysfunction of the single ventricle. Nearly, 50% of patients undergoing repair of tetralogy of Fallot have isolated diastolic RV dysfunction [24], and may develop LCOS due to insufficient preload of the LV. High PVR results in dysfunction of the cavo-pulmonary anastomosis following a bidirectional Glenn or a Fontan procedure, to a decrease of the single-ventricle preload, and to LCOS (Boxes 21.2 and 21.3).

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Box 21.2: Factors responsible for a postoperative decrease in DO_2

- LCOS due to:
  - Increased LV and/or RV afterload
  - Myocardial stunning
  - Pulmonary endothelium dysfunction
  - Underlying CHD-specific causes
- Hypoxemia
- Anemia

Box 21.3: Limitations of the cardiovascular reserve in neonates

- Decreased contractile reserve
- Cardiomyocyte contains fewer and poorly organized proteins
- Immature sarcoplasmic reticulum
- Decreased myocardial compliance
- Increased circulatory demands due to greater oxygen consumption

Source: From [18].

KEY POINTS: THE VO_2/DO_2 BALANCE FOLLOWING CHD SURGERY

- Pathologic imbalance between VO_2 and DO_2 is the mechanism of anaerobic metabolism, multiorgan failure, and death.
- VO_2 commonly increases after CHD surgery mainly due to inflammation and postoperative stress response.
- DO_2 commonly decreases after CHD surgery mainly due to LCOS, a result of inflammation, myocardial stunning, and pulmonary dysfunction.

Improving postoperative oxygen transport balance: preventive and therapeutic interventions

As mentioned before, the goal of the postoperative hemodynamic manipulation is the optimization of the VO_2/DO_2 balance. Sedation and analgesia lead to substantial falls in postoperative VO_2 [11], which could suffice to maintain the VO_2/DO_2 balance in critical situations where it is not possible to further increase the DO_2. Treatment of hyperthermia reduces the VO_2 by 11% for every degree of reduction in body temperature [11]. Anti-inflammatory strategies have been reported to have similar effects, probably by acting on both the inflammatory state and hyperthermia [25]. In addition, mechanical ventilation with muscle relaxation reduces VO_2 by more than 20%, and as well as stabilizing pulmonary gas exchange, it can preserve the limited DO_2 for other vital organs [13]. On the other hand, blood transfusions cause a significant increase in DO_2; transfusion thresholds are specific to age and dependent upon the underlying CHD; and limitations are due to increases in blood viscosity and PVR.

The major priorities, nevertheless, both intra- and postoperatively, are the prevention and early treatment of the LCOS, and this section will focus on the pharmacological treatment of LCOS. The pharmacologic optimization of CO in children with cardiac surgery involves the manipulation of systolic and diastolic myocardial function, preload, SVR, and PVR.

The prospective study published by Wernovsky et al. in 1995 [3], including invasive hemodynamic measurements in 122 neonates undergoing the arterial switch operation, demonstrated an average 30% drop in cardiac index in almost one quarter of patients, while PVR and SVR increased. The lowest measurement typically occurred 9–12 hours after surgery. Evidence supporting preventive drug therapy for LCOS is derived primarily from the landmark PRIMACORP study [4], which reported a 55% reduction in the risk of postoperative LCOS after administration of high-dose milrinone. As a result, preventive drug therapy for LCOS in at-risk patients has become common practice, as revealed by two recent international surveys among pediatric cardiac centers [26, 27].

The ventricular pressure–volume loops shown in Figure 21.2 illustrate the possible therapeutic options to increase the stroke volume in case of a reduced CO with increased afterload. Increasing preload results in an increase in the stroke volume according to the Frank–Starling law, with a concomitant increase, however, in the workload of the ventricle. Ischemia–reperfusion injury and myocardial edema resulting from aortic cross-clamping aggravates the physiological stiffness of the neonatal myocardium, and it follows that the beneficial potential of volume administration is limited by an excessive increase in the atrial pressure. Inotropic agents augment the stroke volume too, however, their benefit is limited by the concomitant increase in the workload, and thus VO_2, of the ventricle. By contrast, vasodilators increase the stroke volume without affecting myocardial oxygen demand, and represent, therefore, the most effective option in the setting of postcardiac surgery LCOS in infants.

In the pediatric cardiac setting, the use of cardiovascular drugs is often based on extrapolating the underlying pathophysiology and pharmacodynamics from adult studies, and on anecdotal experience. In 2008, Pasquali et al. published a survey on the use of off-label cardiovascular medications in children as assessed by the Pediatric Health Information System [28]. The study included observations from 31,432 patients, median age 10.4 months, and reported that 78% of all patients received at least one cardiovascular drug off-label. The risk of a neonate receiving at least one drug off-label was 11% higher than that of an older patient. The most common cardiovascular drugs used off-label were furosemide, epinephrine, dopamine, lidocaine, and milrinone. It is also important to note that there are no clinical trials that have produced recommendations with regards to dosing. Therefore, the suggested dose ranges here should be considered as "guides."

The drugs currently used for the acute hemodynamic management of CHD patients have inotropic, chronotropic, lusitropic, vasoconstrictor, systemic, and/or pulmonary vasodilator effects. Most of the cardiovascular drugs have mixed and dose-dependent effects, therefore, a functional classification has been proposed, according to their inotropic and peripheral vascular effects into: inodilators, inoconstrictors, vasodilators, and vasoconstrictors [29]. The most commonly used agents are displayed in Table 21.1 and Figure 21.4, according to their potencies and dose-dependent hemodynamic effects.

Most cardiovascular agents in clinical use exert their cardiovascular effects by interacting with adrenergic receptors in the heart and vessels. Vascular α_1-adrenergic receptors increase SVR by constricting the mesenteric, skin, and renal

Table 21.1 Classification of the most popular inotropic and vasoactive agents

Peripheral vascular effect	Inotropic effect	
	Yes	No
Vasoconstriction	**Inoconstrictors**	**Vasoconstrictors**
	Epinephrine Dopamine	Norepinephrine Vasopressin Phenylephrine
Vasodilation	**Inodilators** Milrinone Dobutamine Levosimendan	**Vasodilators** Nitroglycerin Nitroprusside Phenoxybenzamine

(Source: Adapted from Jentzer et al. [29].)

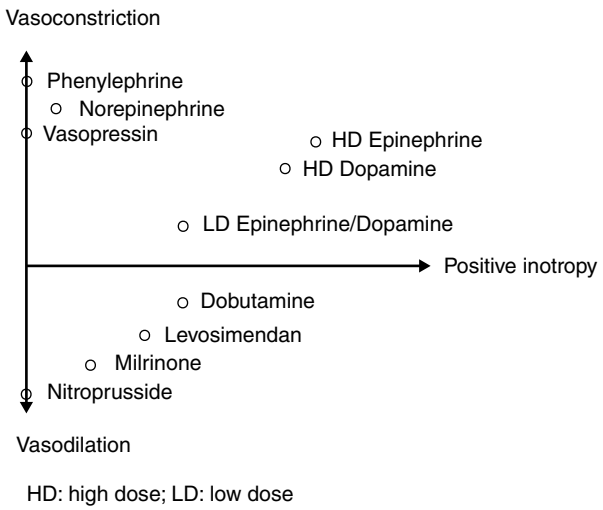


Figure 21.4 Hemodynamic responses to vasoactive and inotropic drugs. (Source: Adapted from Jentzer et al. [29].)

arterioles while redistributing blood flow from the peripheral veins into the arterial circulation. Myocardial β_1 receptors, and to a lesser extent, β_2-adrenergic receptors, increase HR and cardiac contractility. Vascular β_2 receptors, and to a lesser extent, β_1 receptors, oppose the vasoconstrictive effects of α_1 receptors and reduce vascular tone, especially in the skeletal muscle. The location and effects of adrenergic receptors are shown in Table 21.2. Vasopressin 1a receptors (V_{1a}) mimic and augment the vasoconstrictive effect of α_1 receptors.

Table 21.2 Adrenergic receptor sites and physiologic actions

Receptor	Receptor location site	Action
α_1	Vascular smooth muscle	Arterial vasoconstriction
	Heart	↑ inotropic activity
α_2	Vascular smooth muscle	Vasoconstriction of venous capacitance vessels
	Presynaptic sympathetic nerve terminals	Local feedback, inhibition of norepinephrine release
β_1	Heart	↑ inotropic and chronotropic activity ↑ atrio-ventricular node conduction velocity
β_2	Vascular smooth muscle	Vasodilation peripheral vasculature
	Bronchial smooth muscle	Bronchodilation
D_1	Vascular smooth muscle (renal, splanchnic, cerebral)	Vasodilation
	Renal tubules	↓ Na reabsorption
D_2	Presynaptic sympathetic nerve terminals	↓ norepinephrine release

(Source: From Latifi et al. [30].)

Inotropic agents

The most commonly used inotropic agents are β-adrenergic agonists (catecholamines) and phosphodiesterase type 3 inhibitors. These agents exert positive inotropic and chronotropic effects by increasing the intracellular calcium concentration via an increase in cyclic adenosine monophosphate (c-AMP) and activation of the protein kinase pathway in cardiac myocytes, as shown in Figure 21.5. c-AMP, in turn, activates calcium channels and lead to increased cytosolic calcium, which improves the contractility of the actin–myosin system through its binding with troponin C. A newer class of inotropes is calcium sensitizers, which binds cardiac troponin C, stabilizes calcium-induced conformational changes, and increases contractility by promoting a prolonged interaction between actin and myosin filaments. They do not increase cytosolic calcium concentrations.

β-adrenergic receptor agonists

Catecholamines play an important role in the management of LCOS after cardiac surgery. Endogenous catecholamines, such as dopamine, epinephrine, and norepinephrine, are synthesized from tyrosine, which undergoes several transformations to yield dopamine. A portion of the dopamine is then transported into vesicles from the cytoplasm where it is converted to norepinephrine, the main neurotransmitter in the human nervous system. The final step in the pathway,

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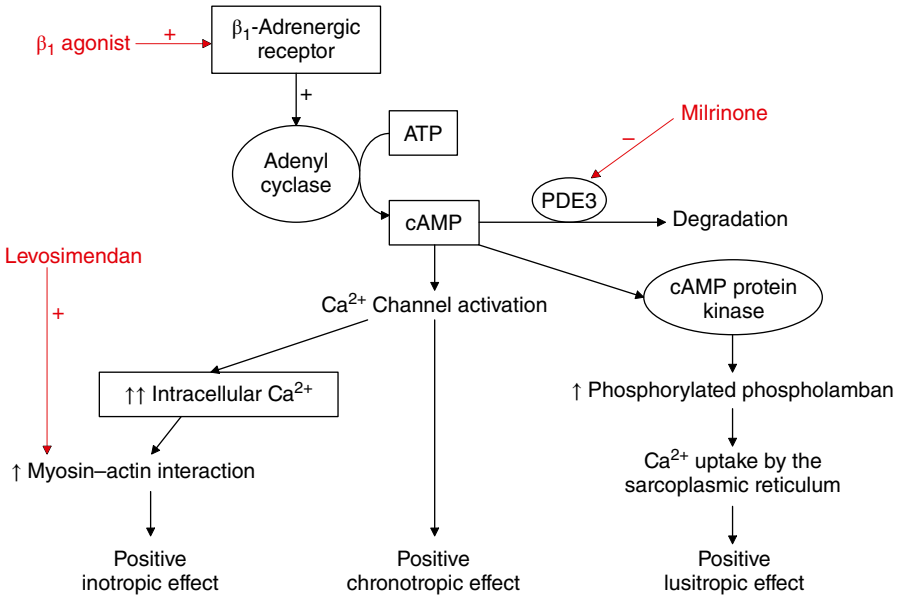


Figure 21.5 Schematic representation of the postulated mechanism of action of β_1-agonists, milrinone and levosimendan in the myocardial cell. (Source: Gillies et al. [31]. Reproduced with permission of Springer Nature.)

Table 21.3 Hemodynamic effects of the most popular vasoactive and inotropic drugs

Drug	Receptors	Inotropy	Chronotropy	SVR	PVR	Renal vascular resistance	Cardiac output
Epinephrine < 0.1 μg/kg/min	β_1, β_2 > α_1 (agonist)	↑	↑	↔ ↓	↔ ↓	↓	↑↑
>0.1 μg/kg/min	α_1 > β_1, β_2	↑	↑	↑	↑	↑	↑
Dopamine < 3 μg/kg/min	D_1, D_2 (agonist)	↔	↔	↔	↔	↓	↔
4–8 μg/kg/min	β_1, β_2 > α_1	↑	↑	↔ ↓	↔	↔	↑
>8 μg/kg/min	α_1 > β_1, β_2	↑	↑	↑	↑	↑	↔
Dobutamine	β_1 > β_2, α_1 (agonist)	↑	↑	↓	↓	↔	↑↑
Milrinone	PDE3 inhibitor	↑	↑	↓	↓	↓	↑
Levosimendan	Troponin C, ATP-dependent K channel	↑	↑	↓	↓	↓	↑
Norepinephrine	α_1 > β_1, β_2 (agonist)	↔ ↑	↓	↑↑	↑	↑↑	↔ ↓
Vasopressin	V_{1a} (agonist)	↔	↓	↑	↑	↑	↔ ↓
Phenylephrine	α_1 (agonist)	↔	↓	↑	↔	↑	↔ ↓
Nitroglycerine Nitroprusside	Guanylate cyclase activator	↔	↔ ↑	↓	↓	↓	↑
Phenoxybenzamine	α_1, α_2 (antagonist)	↔	↔ ↑	↓	↓	↓	↑
Inhaled Nitric oxide	Guanylate cyclase activator	↔	↔	↔	↓↓	↔	↔ ↑
Sildenafil	PDE5 inhibitor	↔	↔	↔	↓↓	↔	↔ ↑

ATP: adenosine triphosphate; c-AMP: cyclic adenosine monophosphate; PDE3: phosphodiesterase type 3; PDE5: phosphodiesterase type 5; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.

which converts norepinephrine to epinephrine, occurs in the adrenal medulla. Endogenous catecholamines are hormones and neurotransmitters that influence a multitude of physiological functions; however, synthetic catecholamines, such as dobutamine and isoproterenol, target-specific receptors resulting in selective effects (Table 21.3). The half-life of catecholamines is approximately 2–5 min, which allows for rapid titration. Since the breakdown of catecholamines by the catechol-O-methyl-transferase and monoamine oxidase is ubiquitous, dosage adjustments are not necessary, even in patients with renal, hepatic, or any other organ dysfunction.

Epinephrine

Epinephrine has a potent agonist of α_1-, β_1-, and β_2-adrenergic receptors (Table 21.3), approximately 100-fold more potent as an inotrope than dobutamine or dopamine. Low epinephrine doses (0.01–0.1 μg/kg/min) are used to increase stroke volume and to a lesser extent HR through a β_2-adrenergic effects. Combined with afterload reduction through peripheral vasodilatation, low epinephrine doses increase CO, and is therefore recommended in patients with severe systolic dysfunction. At somewhat higher concentrations, β_1-adrenergic receptors are activated resulting in increased myocardial

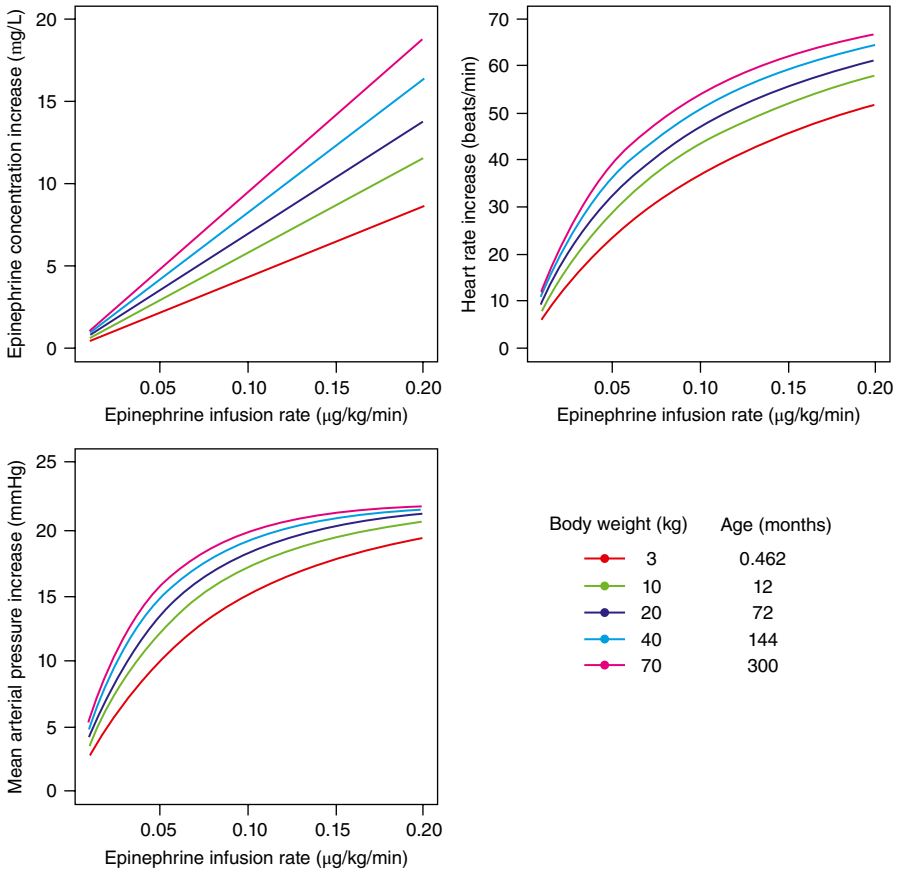


Figure 21.6 Simulation of the relationship between different epinephrine concentrations and hemodynamic responses in children with different ages and weights. (Source: Oualha et al. [33]. Reproduced with permission of Springer Nature.)

conduction, increased sinoatrial node discharge, increased force of contraction, and increased rate of rise of the intramural pressure. High concentrations of epinephrine may produce serious atrial and ventricular dysrhythmias if the myocardium is sensitized by infarction, surgery, or myocarditis. Higher epinephrine doses (>0.1 μg/kg/min) produce increasing α_1-receptor-mediated vasoconstriction. This results in increased afterload and increase the myocardial workload, which are undesirable early after CPB, and may be detrimental in infants with functionally univentricular circulation. Even though epinephrine constricts renal and cutaneous arterioles, renal function and skin perfusion may improve due to increased CO. However, high infusion rates (>1–2 μg/kg/min), conditions in which the α_1-adrenergic responses predominate, may exacerbate multiorgan system failure.

Epinephrine is largely used in the postoperative management of CHD [26, 32], although evidence-based data are currently lacking, and dosing regimens are extrapolated from adult studies. However, the amplitude of the hemodynamic response to epinephrine is difficult to predict. Although the effect of epinephrine is primarily dependent on the plasma concentration, a recent report shows that both age and body weight may play a role in the large between-subject pharmacokinetic and pharmacodynamic variability observed in children undergoing CHD surgery [33]. The smaller the patient, the smaller the increase in heart rate and blood pressure for a given epinephrine concentration and severity of illness, as shown in Figure 21.6 [33]. It is likely that the postnatal development of the myocardial contractility is associated with changes in the modulatory effects of β-adrenergic receptor signaling.

During cardiopulmonary resuscitation, the α_1-adrenergic-mediated vasoconstriction induced by epinephrine increases aortic diastolic pressure and, thus, coronary perfusion pressure, which is a critical determinant of successful resuscitation from cardiac arrest. The American Heart Association-recommended dose of epinephrine for children experiencing bradycardia, asystole, or pulseless arrest is 0.01 mg/kg intravenously, which may be repeated at 3–5-min intervals, up to 1 mg per dose [34].

Dopamine

Dopamine stimulates the dopaminergic D_1 (postsynaptic) and D_2 (presynaptic) receptors located in several vascular beds; it also binds α- and β_1-adrenergic receptors, although with lower affinity (Table 21.3) doses (> 8 μg/kg/min) induce vasoconstriction via α_1-adrenergic receptor stimulation. Increased PVR has been reported with dopamine doses higher than 7.5 μg/kg/min.

The sensitivity of infants to dopamine is controversial, and neonates may exhibit a clinical response to doses as low as 0.5–1 μg/kg/min [30]. Li et al. [35] studied the effects of 5 μg/kg/min of dopamine in neonates undergoing the Norwood

procedure. Dopamine did not increase DO_2 and seemed to cause an increase in myocardial VO_2. A dopamine infusion of 5 μg/kg/hour had a significant thermogenic effect, and termination of the infusion was associated with a substantial 20% reduction in the total VO_2 [35].

Dobutamine

Dobutamine is administered as a racemic mixture of two compounds, namely, a strong β_1-agonist, and a weak α and β_2 agonist. The end result is a drug with broad receptor specificity, a strong dose-dependent increase in stroke volume, heart rate and CO, and a variable effect on arterial pressure (Table 21.3). It modestly lowers the SVR, except at high doses (> 10–15 μg/kg/min) when dose-dependent α_1-adrenergic receptor agonism may become more prominent. Low doses, up to 5 μg/kg/min, increase stroke volume without significant tachycardia, however, doses above 10 μg/kg/min produce worsening tachycardia with minimal further increase in CO due to declining stroke volume from decreased diastolic filling time. Dobutamine significantly increases the myocardial VO_2 and is frequently used to stress the myocardium.

Comparison with phosphodiesterase inhibitors demonstrates similar improvement in stroke volume, although dobutamine induces a more profound decrease in LV filling pressures and vascular resistance [36]. Dobutamine induces a greater increase in heart rate than milrinone, and the beneficial increase in coronary blood flow may be outweighed by an increase in myocardial VO_2 [36]. Higher doses of dobutamine (>15 μg/kg/min) can predispose to the development of atrial or ventricular arrhythmias. Despite its widespread use, the exact role of dobutamine in pediatric therapeutics remains unclear, and its use following cardiac surgery remains controversial because of excessive tachycardia, arrhythmias, and variable effect on SVR.

Norepinephrine

Norepinephrine is a potent α_1-receptor agonist and mild β_{1-} agonist with minimal β_2 activity. Increasing doses of norepinephrine may increase CO in some patients through augmentation of venous return, however, it may reduce CO due to the strong increase in afterload in patients with cardiac dysfunction. Norepinephrine reduces myocardial VO_2, due to a reflex reduction in heart rate. By increasing diastolic pressure, norepinephrine increases coronary perfusion. Norepinephrine is mainly used as a vasopressor and will be discussed later.

Side effects of catecholamines

The use of catecholamines comes at a price, namely to place continual stress on an organ that is already failing, and placing an increased demand for oxygen at a time when supply is critically limited. Catecholamines increase the myocardial VO_2 through their inotropic and chronotropic effects and induce arrhythmogenesis. These are due to an increase in intracellular calcium concentration, produced by an increase in c-AMP. This is particularly problematic in the neonatal myocardium, in which the functional reserve is limited and which operates under already maximal adrenergic stimulation. If such an increase is not accompanied by a proportional increase in coronary blood flow, a mismatch between myocardial VO_2 and DO_2 may result.

When inotropes are used for the management of adults with acute heart failure, there is an increase in in-hospital mortality when compared with management without inotropes [37]. Results from the European Society of Cardiology Heart Failure Long-term registry have shown a detrimental association between the use of inotrope and/or vasopressor and both in-hospital and long-term mortality [38]. Both dopamine and epinephrine were associated with the highest risk of death in adults [38, 39]. The recent guidelines of the European Society of Cardiology for the treatment of acute heart failure restrict the use of inotropic agents to patients with symptomatic hypotension and poor perfusion [40].

For many years, it has been acknowledged that chronic exposure to catecholamines can exert a toxic effect on the myocardium and increase apoptosis. *In vitro* studies in cultured cardiac myocytes show that tonic exposure to norepinephrine increases the number of apoptotic myocytes via stimulation of the β_1-adrenergic receptor pathway [41]. Although the link between myocardial apoptosis and myocardial failure remains to be proven, these observations provide a rational to limit the use of β_1-agonists following cardiac surgery. In addition, the variability in the pharmacologic effect of β-agonists in neonates makes their use very challenging in this age group. Studies of myocardial biopsies identified an adult-like myocardium, with low-density and high-affinity β-adrenergic receptors, and a fetal-like myocardium, with high-density and low-affinity β-adrenergic receptors [42]. Neonates had the highest density and the lowest affinity β-adrenergic receptors of all, and they have lower affinity β receptors in the LV when compared with the RV (whereas immature and adult hearts did not have ventricular differences) [42]. Additionally, experimental studies demonstrated downregulation of the LV β-adrenergic receptors during chronic hypoxemia [43].

Long-term exposure of myocardial β-adrenergic receptors to circulating endogenous or exogenous catecholamines leads to receptor desensitization, which is mediated by uncoupling of the receptor–effector system and by a decrease in receptor density. In patients with severe cardiac failure, β_1-adrenergic receptor density is selectively reduced due to exposure to endogenous norepinephrine. It has been shown that the severity of the left-to-right shunt and of PHT is correlated with norepinephrine levels in pediatric CHD patients [44]. Consistently, children with severe CHD were found to have an up to 50% reduction in the number of right auricle β-adrenergic receptors, with the lowest receptor densities found in critically ill neonates with congenital aortic stenosis and transposition of the great arteries [45].

Catecholamines increase the overall metabolic rate, which manifests as an increase in the overall VO_2. β_1, β_2, and particularly β_3-adrenergic receptors, as well as dopaminergic receptors are densely expressed at high levels in brown adipose tissue, which is abundant in human neonates, where it plays a crucial role in nonshivering thermogenesis. Catecholamines, especially norepinephrine and dopamine, simulate heat production by stimulating fatty acid oxidation and uncoupling the respiratory chain from adenosine triphosphate (ATP)

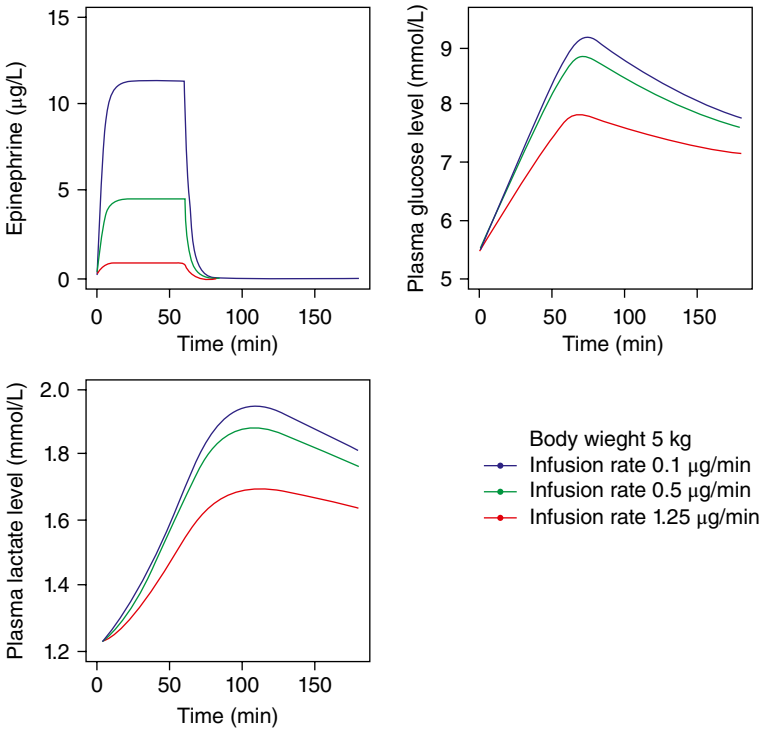


Figure 21.7 Time-course simulations of epinephrine concentration, plasma glucose and lactate levels following 0.02–0.25µg/kg/min epinephrine infusions in a child weighting 5 kg. (Source: Oualha et al. [33]. Reproduced with permission of Springer Nature.)

synthesis; thus, neonates may be particularly susceptible to the metabolic effects of catecholamines, which may increase VO_2 to much higher levels than in older patients. Catecholamines also accelerate aerobic glycolysis and induce insulin resistance, a phenomenon that is exacerbated in younger patients, resulting in a concentration-dependent increase in glycemia and lactate production, as shown in Figure 21.7 [33].

In view of the aforementioned challenges, the use of β-adrenergic receptor agonists for the prevention and/or management of LCOS following CHD surgery should be questioned, particularly considering that the evidence of their use is based solely on pharmacological action rather than an assessment of meaningful clinical outcomes.

Inhibitors of phosphodiesterase type 3

Bipyridines were developed in the 1980s to improve myocardial contractility in the chronically failing ventricle. They selectively inhibit intracellular cardiac phosphodiesterase type 3, thereby slowing the degradation of c-AMP. This results in a positive inotropic effect through increased intracellular calcium levels during excitation–contraction coupling, and a positive lusitropic effect through faster sequestration of calcium that is released into the sarcoplasmic reticulum due to the concomitant activation of phospholamban (Figure 21.5). Vasodilation occurs in both arterial and venous vessels, via increased c-AMP and opening ATP-sensitive potassium channels in vascular smooth muscle cells (Figure 21.8). Arrhythmogenicity is mediated by an increase in intracellular c-AMP and calcium levels. No tachyphylaxis is observed.

Amrinone

Amrinone, the prototype bipyridine, acts mainly as a vasodilator, and has some inotropic effects [47–49]. Amrinone is metabolized in the liver via N-acetylation and is then excreted in the urine; slow acetylators show a two-fold increase in the half-life, compared with that of rapid acetylators [50]. The half-life is about 2 hours, and clearance is reduced in patients with hepatic and renal failure. Reversible dose-dependent thrombocytopenia is common during prolonged therapy. The common dosage is 5–10 µg/kg/min. Amrinone is now rarely used since milrinone became available.

Milrinone

Milrinone is the most popular bipyridine drug, and it is the one that has been subjected to careful evaluation in the placebo-controlled multicenter PRIMACORP trial [4]. It has a half-life of about 1 hours, which decreases linearly with age and increases in the presence of renal failure [51].

The drug shows inotropic and vasodilatory effects, although it appears that the increase in CO is mainly related to the vasodilatory effect [52]. Chang et al. reported that, when given to neonates with LCOS, milrinone increased the cardiac index from 2.1 to 3.1 mL/min/m^2, concomitant with a reduction in filling pressures, in SVR by approximately 30%, and in PVR by about 25% [53]. These improvements in global hemodynamics were associated with an improvement in the myocardial VO_2/DO_2 ratio [53]. The multicenter PRIMACORP trial [4], including 238 neonates and infants demonstrated that the prophylactic administration of high-dose milrinone (i.e., a bolus of

75 μg/kg, followed by an infusion of 0.75 μg/kg/min) decreased the incidence of LCOS from 25.9% to up to 11.7%, whereas a low dose (a 25 μg/kg/min bolus followed by a 0.25 μg/kg/min infusion) had no effect, when compared with placebo.

In an experimental study under constant ventricular leading conditions, milrinone only very slightly increases heart rate and stroke volume [52]. Thus, unlike dopamine, milrinone does not increase myocardial VO_2 [36] nor myocardial OER (17). Instead, milrinone reduces coronary vascular resistance, suggesting that it exerts a protective effect on the myocardium. Furthermore, the positive lusitropic properties make milrinone a useful drug when LCOS results from diastolic ventricular dysfunction.

The pulmonary vasodilator effect of milrinone has been demonstrated in infants with PHT, and it is largely dependent on the degree of pre-existing PHT and the severity of ventricular dysfunction [53]. Milrinone induces pulmonary vasodilatation by increasing pulmonary vascular c-AMP levels, and, possibly, by attenuating the release of inflammatory cytokine [54].

Hypotension is a commonly reported side effect, occurring particularly during the administration of the loading dose. Ensuring an adequate preload can minimize it. The incidence of tachyarrhythmia increases up to three-fold when using common dosing regimens of milrinone (a loading dose of 50 μg/kg, followed by a 0.25–1 μg/kg/min continuous infusion), independent of the concomitant use of catecholamines and of disease severity. As a result, many centers use milrinone without a loading dose, and begin the infusion by the end of CPB. However, a recent pharmacokinetic study of milrinone in a wide pediatric age range demonstrated that age, disease, and surgery differently impact the pharmacokinetics of milrinone, and that current milrinone dosing for LCOS is suboptimal to maintain the therapeutic target range across the entire pediatric age range [55]. It is likely that hypotension and arrhythmogenesis are responsible for the huge variability in the dosing regimens used at different centers [32]. Thrombocytopenia is less common (4%) and is seen when the infusion duration exceeds 3 days [56].

Milrinone is the drug most commonly used for the prevention and treatment of LCOS in CHD surgery [26, 27, 32]. However, the recent Cochrane meta-analysis on its prophylactic use following CHD surgery [57] yielded a very disappointing conclusion indicating a lack of evidence of effectiveness on the incidence of LCOS and on mortality. For methodological reasons, the meta-analysis excluded many valuable reports, and included only 393 participants from a mixed population aged 0–12 years. However, because of their specific physiology, including noncompliant ventricles and a high baseline sympathetic tone [58], neonates and young infants are the most likely to develop LCOS with high SVR and PVR, and to benefit from prophylactic milrinone.

Calcium sensitizers

Levosimendan, a pyridazinone–dinitrile, binds cardiac troponin C and stabilizes calcium-induced conformational changes, which, in turn, promotes the prolonged interaction between actin and myosin filaments during systole, and increases myocardial contractility, as shown in Figure 21.5 [59]. The resulting increase in contractility is unmatched by milrinone [21]. Levosimendan has vasodilatory effects, which are mediated by opening ATP-sensitive potassium channels in the systemic, pulmonary, and coronary vascular smooth muscle cells [59–61]. In adult patients, levosimendan is responsible for a 45% increase in the coronary blood flow and a 9% reduction in myocardial oxygen extraction [62]. The impact of levosimendan on mitochondrial functions prevents calcium overload during ischemia–reperfusion injury and protects the myocardium against damage [63]. Levosimendan reduces the time constant for diastolic relaxation and improves diastolic function [21]. By improving the diastolic function, it is of particular interest when LCOS is due to LV or RV diastolic dysfunction, a common finding in patients with residual obstruction of the left or right outflow tract. It is also of particular interest in neonates in whom the ventricles are less compliant. Levosimendan has weak pulmonary vasodilator effects in the normal circulation [64], but has a potent effect in preconstricted pulmonary circulation [60]. In addition, it may attenuate endothelin-1-induced vasoconstriction, which would be of particular relevance in the post-CPB setting [61]. Experimental work demonstrated an increase in the RV myocardial efficiency when levosimendan was used to treat RV hypertrophy and failure [65], and it has been proposed for the treatment of RV failure in patients with PHT [66]. When given after cardiac surgery in adults, levosimendan is associated with an approximately 50% reduction of the risk of acute kidney injury and renal replacement therapy [67]. Finally, levosimendan improves the recovery of diaphragmatic dysfunction and increases the chances of successful weaning from mechanical ventilation [68].

The pharmacokinetic profile of levosimendan, which is unaffected by age, makes it highly attractive for clinical use. The recommended dosage is an intravenous (i.v.) bolus of 12 μg/kg over 10 min, followed by a 2 μg/kg/min continuous infusion. Its biotransformation in the intestinal tract gives rise to an intermediate metabolite, OR 1,855, which is inactive, and which is further metabolized in the liver by acetylation into OR 1,896. OR 1,896 is a long-lasting active metabolite whose concentration peaks at 36 hours after a 24-hour infusion and remains stable up to Day 8; it is still detectable up to 12 days after levosimendan withdrawal [69]. Dosing adjustments are not required in patients with mild hepatic or renal failure.

A randomized controlled study of milrinone and levosimendan conducted in neonates [69] showed that patients in the milrinone group had a greater requirement for other inotropes during the first hours postsurgery. Cerebral regional saturation monitoring suggested that both drugs caused a time-dependent improvement in blood flow and oxygen availability, but infants on levosimendan showed significantly higher peripheral intravascular oxygenation and a lower difference in the central-to-peripheral temperature gradient [69]. Another randomized controlled trial in neonates undergoing complex surgeries reported an almost 40% decrease in the incidence of LCOS when compared with more conventional milrinone and epinephrine infusions, along with a significant reduction in lactate concentrations 6 hours postoperatively [70]. In patients younger than 5 years

undergoing cardiac surgery, levosimendan given postoperatively was at least as efficacious as milrinone, and did not increase myocardial VO_2 at 24 and 48 hours postoperatively [71]. Troponin values were significantly lower in the levosimendan group, suggesting a cardioprotective effect [71].

Because levosimendan does not increase the intracellular c-AMP and calcium concentrations, tachycardia and hypotension are less severe than that reported for milrinone, although common during the loading dose [69, 71]. In contrast to those of catecholamines, the effects of levosimendan are not attenuated in patients with chronic heart failure, in whom β-adrenergic receptors are downregulated, or by concomitant use of β-blockers. The development of tolerance has not been reported to date.

There are currently no official indications regarding the use of levosimendan in patients less than 18 years of age. As a matter of fact, the drug has been studied and used as a rescue therapy both in the pediatric intensive care unit (PICU) and the operating room. The pediatric experience with levosimendan given prophylactically for cardiac surgery in children less than 5 years was summarized in a recent meta-analysis [72], which, for methodological reasons, only included five randomized controlled trials with a total of 212 participants. Compared with standard inotrope treatments, levosimendan did not reduce mortality or the incidence of LCOS; however, levosimendan significantly reduced time to extubation and length of stay and reduced the risk of circulatory support and of heart transplantation. Levosimendan has potential appeal in children with CHD and may prove to have an important role in the prevention and early treatment of LCOS in high-risk patients after cardiac surgery; however, its application warrants more detailed investigation.

Vasoconstrictors

Norepinephrine

Norepinephrine has potent α- and β_1-adrenergic receptor agonist activity, but little β_2 activity, as shown in Table 21.3. Therefore, infusion of norepinephrine results in increased SVR because the α-adrenergic stimulation is not opposed by β_2-adrenergic stimulation. As a vasopressor, norepinephrine is 100-fold more potent than dopamine and three to five times more potent than epinephrine.

Norepinephrine is used in the pediatric setting of shock with profound hypotension; it should be administered after intravascular volume repletion, and its use is best guided by knowledge of the CO and SVR. Although more commonly used in adults, a vasodilatory inflammatory response to CPB may be present in some children early after surgery and is often responsive to norepinephrine. Norepinephrine may also enhance coronary flow in patients with diastolic run-off after systemic-to-pulmonary shunt. The dosage is usually titrated to mean or diastolic arterial pressure, and low doses (0.01–0.05 μg/kg/min) should be sufficient for hemodynamic stabilization.

However, injudicious use of norepinephrine compromises blood flow within organs, for example, renal, splanchnic, and hepatic blood flow is reduced in healthy individuals. Infusion of norepinephrine may increase blood pressure, and yet not improve clinical indices of perfusion, and this type of poor clinical response is usually associated with a persistent low cardiac index. Importantly, the pharmacokinetics of norepinephrine in children is not well known. Norepinephrine should be titrated and used at the lowest dose to maintain the mean arterial pressure; doses > 0.5–1 μg/kg/min are considered very high.

Arginine vasopressin

Arginine vasopressin (AVP) plays a vital role in the maintaining normal arterial blood pressure by regulating venous capacitance and arterial resistance. Vasopressin acts on V_{1a} receptors in the peripheral vasculature to cause intense vasoconstriction through activation of protein kinase C (Table 21.3), ultimately leading to an influx of intracellular calcium. The rationale behind the use of exogenous AVP in the critically ill patients is that neurohypophyseal stores of AVP may become exhausted, leading to vasodilatory shock [73]. Another theoretical advantage of AVP is that it does not rely on adrenergic receptors, which may be downregulated in the presence of chronically elevated catecholamines. Also, signal transmission via adrenergic receptors may be impaired under conditions of metabolic acidosis. AVP depletion following CHD surgery has also been reported in children [74], as well as good response to the vasopressor AVP infusion ranging from 0.0001 to 0.002 U/kg/min in neonates, infants, and children with low postoperative blood pressure and adequate cardiac function [74, 75]. More recently, it has been suggested that lower doses of AVP 0.0003 U/kg/min initiated in the operating room could be beneficial in neonates with complex surgeries, such as the Norwood procedure or the arterial switch operation, to decrease the requirement for fluid resuscitation and catecholamines, and shorten the duration of intensive care stay [76].

A recent meta-analysis showed that AVP did not confer a survival advantage in adults suffering from vasodilatory shock [77]. Also, safety data for AVP are lacking; a prospective randomized study of critically ill children requiring prolonged mechanical ventilation showed that AVP was associated with an increased incidence of oliguria and hyponatremia [78].

Phenylephrine

Phenylephrine is a pure peripheral α_1-adrenergic receptor agonist, as shown in Table 21.3, and is used as a bolus or infusion to treat acute cases of low systemic blood pressure or SVR. The pure α_1 effects can result in reflex slowing of the heart rate, although this is not as pronounced in young infants as it is in adults. Its main use in CHD is to acutely raise SVR in cases where either ventricle is compromised by outflow obstruction. Such is the case of tetralogy of Fallot, where low SVR lead to increased right-to-left intracardiac shunting and cyanosis, and in hypertrophic cardiomyopathy or other left-sided lesions, in which the gradient across the obstruction is increased by low SVR. A bolus dosing of phenylephrine, such as used on CPB to increase perfusion pressure, is 0.5–5 μg/kg, whereas infusion doses range from 0.02 to 0.3 μg/kg/min.

Systemic vasodilators

The tolerance of systemic vasodilators is affected by the intravascular status, or by any actual or potential outflow

tract obstruction; in such cases, systemic vasodilatation may have disastrous consequences. Careful imaging should be performed to exclude outflow tract obstruction in case of a doubt, prior to administering the vasodilator, and a very low dose or a short acting agent should be given first.

Nitric oxide donors: nitroglycerin and sodium nitroprusside

Nitric oxide donors mimic the effect of endogenous NO, and by activating guanylate cyclase they lead to increased cyclic guanosine monophosphate (c-GMP) production and vasodilation (Table 21.3). Low-to-moderate doses of nitroglycerin (3 μg/kg/min) increase venous capacitance without affecting the arterial resistance vessels [79]. As a result, ventricular filling pressures fall, whereas the stroke volume is unaffected. High-dose nitroglycerin and nitroprusside increase venous capacitance and reduce SVR; thus, filling pressures fall and the stroke volume and CO rise significantly. Major indications for the use of nitroglycerin include myocardial ischemia, systemic hypertension, volume overload, congestive heart failure, and pulmonary edema. The net effect is usually an improvement in the myocardial VO_2/DO_2 ratio. Efficacy has been demonstrated following CHD surgery [80].

Tolerance occurs after more than 24 hours of i.v. therapy, and abrupt weaning after prolonged i.v. infusions may result in rebound hypertension. Extremely rare side effects are methemoglobinemia and cyanide toxicity, which result from the release of nitrite ions when the drug is metabolized.

Phenoxybenzamine

Phenoxybenzamine is a long acting α_1- and α_2-adrenergic receptor blocker, as shown in Table 21.3, and is advocated by some groups for the routine perioperative management of infants undergoing cardiac surgery involving hypothermic CPB. It has gained popularity for infants undergoing the Norwood operation, in whom systemic vasoconstriction occurs additionally in response to failing systemic perfusion (such as seen at $SaO_2 > 80\%$). Such a situation was traditionally managed by manipulating the medical gases to increase PVR and lower SVR. Hoffman et al. carried out a prospective study of phenoxybenzamine use following the Norwood operation [81], where patients received 0.25 mg/kg phenoxybenzamine at the start of CPB, followed by 0.25 mg/kg/24 hours for up to 48 hours postoperatively if the target $SvO_2 > 50\%$ and target Q_P/Q_S ratio of 0.8–1.2 were not reached. There was no evidence of hemodynamic deterioration at high SaO_2 [81], suggesting that α-adrenergic receptor blockade is an effective approach to modifying the intense sympathetically mediated vasomotor responses in these infants. However, the irreversible α-receptor blockade and prolonged effect has limited its popularity.

Phentolamine

Phentolamine is a reversible α-adrenergic receptor blocker. Its use is justified by the observation of elevated plasma catecholamine concentrations and increased SVR following CPB. A randomized trial of phentolamine in CHD surgery reported that administration of 0.2 mg/kg of phentolamine during cooling and rewarming for cardiac surgery reduced plasma lactate levels, indicating better tissue perfusion; in addition, the nasopharyngeal–rectal temperature gradient decreased four-fold, whereas systemic VO_2 increased [82].

Hydralazine

Hydralazine dilates precapillary arterioles. Most studies of hydralazine were performed in the 1980s, in which the drug was used to treat hypertension following CPB in adults. Hydralazine can be used to treat postoperative hypertension in children (1–5 μg/kg/min), or in other situations that require a reduction in preload, such as severe myocardial dysfunction and extracorporeal membrane oxygenation (ECMO). However, the vasodilatory effect is limited by reflex tachycardia; therefore, β-adrenergic receptor blockers and sodium nitroprusside are preferred.

Nesiritide

Nesiritide is a recombinant form of human B-type natriuretic peptide, which is normally produced by the ventricular myocardium. It binds with the A- and B-type natriuretic peptide receptors of the vascular endothelium and smooth muscle, which leads to increased c-GMP production and vasodilation. It increases the glomerular filtration rate and inhibits sodium reabsorption, exerting a strong diuretic effect. Nesiritide was first believed to be beneficial for the treatment of acute decompensated congestive heart failure. Although it has also been found beneficial for the prevention of acute kidney injury following cardiac surgery in adults [83], the results of the largest study performed to date showed that nesiritide does not affect mortality or prevent rehospitalizations in adults [84]. No major hemodynamic effect has been reported when used after CHD surgery [85], but an improved urine output. The recommended dose range for infusion in infants and children with heart disease is 0.01–0.03 μg/kg/min.

Pulmonary vasodilators

In the early 1990s, PHT was a major cause of post-CHD surgery mortality [86]. Overall survival has improved since then and the reported incidence of severe PHT (defined as a ratio of pulmonary-to-systemic arterial pressure >1) has dropped to 2% [87], most likely due to a better understanding of the pathophysiology of PHT, earlier surgical correction in patients at high risk of PHT, and refinement of intraoperative techniques, including ultrafiltration.

It is accepted that an important pathological characteristic of pulmonary vascular reactivity in patients with CHD is dysfunction of the pulmonary endothelium [88]. Such dysfunction suppresses the intrinsic endothelium-dependent vasodilatory mechanisms, including the nitric oxide c-GMP system. c-GMP is generated by the interaction between NO and guanylate cyclase, and it is the final messenger in the pathway that mediates vascular smooth muscle relaxation. It is metabolized by the phosphodiesterase type 5, which is the major phosphodiesterase in the lung; phosphodiesterase type 5 expression is upregulated in patients with PHT and

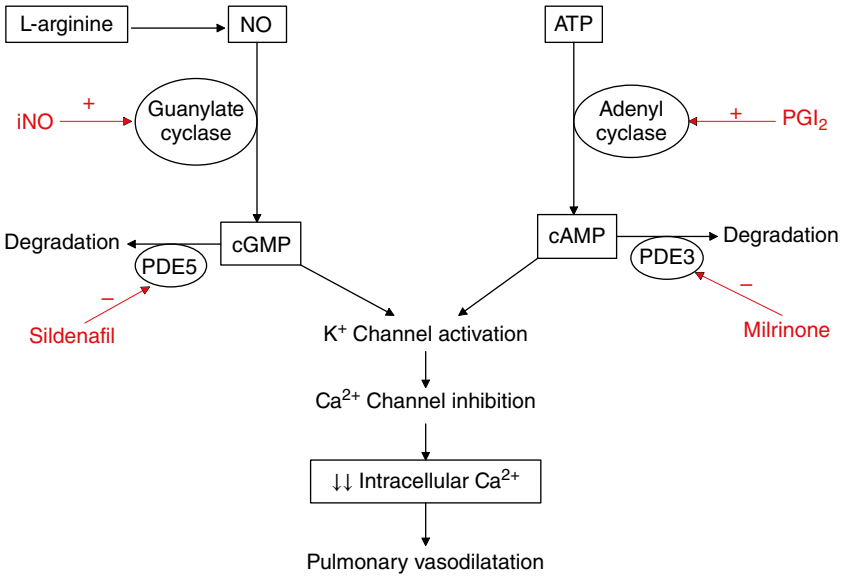


Figure 21.8 Schematic representation of the postulated mechanism of action of pulmonary vasodilators in the endothelial cell. (Source: Adapted from Ghofrani et al. [46].)

after CPB, causing increased turnover of c-GMP. A schematic representation of the mechanism of action of pulmonary vasodilators is shown in Figure 21.8.

Pulmonary vasodilators are commonly used to lower PVR and to treat acute postoperative PHT in patients with preoperative pulmonary overcirculation, or pulmonary venous obstruction. In addition, children undergoing cavopulmonary connections for single-ventricle lesions require low PVR for surgical success. Finally, pulmonary vasodilators are used to reduce the RV afterload, which is often increased following heart transplantation [89]. Historically, the standard therapy for lowering PVR included the induction of respiratory alkalosis due to the known effects of pH on pulmonary artery pressure and PVR; however, although hyperventilation reduces PVR, this comes at the expense of a subsequent increase in SVR and reduction in CO [90]. Other factors are used to lower PVR, including sedation, lung recruitment to improve oxygenation, and metabolic alkalosis.

Inhaled nitric oxide

Inhaled nitric oxide (iNO) has been used for more than two decades to selectively reduce PVR. iNO produces pulmonary vasodilation in ventilated lung regions by activating endothelial guanylate cyclase, resulting in increased levels of c-GMP, which, in turn, relaxes pulmonary vascular smooth muscle. iNO crosses the alveolar–capillary membrane leading to immediate pulmonary vasodilation. High-affinity binding and immediate inactivation of iNO activity by hemoglobin limits the action of the drug in the pulmonary circulation.

An early study by Miller et al. reported that iNO concentrations as low as 2 ppm reduced PVR by approximately 40%, and improved CO by approximately 15% [91]. The pulmonary/systemic artery pressure ratio predicts the response to iNO, with a greater response seen in those with a high ratio (≥0.50). The use of iNO has become more common, and a randomized double-blinded study demonstrated its usefulness as a prophylactic treatment in patients at risk of PHT: patients treated with iNO suffered fewer PHT episodes and could be extubated more quickly [92]. Morris et al. [90] demonstrated that iNO was as effective as hyperventilation for reducing PVR; however, unlike hyperventilation, iNO did not increase SVR or reduce CO. iNO significantly improves oxygenation, lowers the transpulmonary gradient by 40–50%, and reduces central venous pressure by 15–20% in hypoxic patients undergoing Fontan-type procedures [93].

There are inherent problems with iNO, which may limit its use. These include a suboptimal response in some patients, the development of rebound PHT upon withdrawal after even relatively short periods of use, and the mode of delivery, which generally, though not necessarily, requires endotracheal intubation. Moreover, the individual responses to iNO are variable. Abrupt withdrawal of iNO or rapid reductions in the dose may lead to rebound PHT [94], even in patients with no pre-existing PHT. Rebound is due to the downregulation of endogenous NO synthase in the pulmonary vascular endothelium and a reduction in guanylate cyclase activity. Rebound PHT responds to reinstitution of iNO; however, an interesting pharmacological solution is the addition of sildenafil, a selective inhibitor of phosphodiesterase type 5, which prevents the breakdown of c-GMP until c-GMP levels become naturally replete. As such, a single i.v. dose of 0.4 mg/kg sildenafil before weaning from iNO prevents rebound PHT in neonates and infants [95].

iNO has few side effects. However, the binding of NO to hemoglobin gives rise to methemoglobin; therefore, methemoglobin levels should be routinely monitored particularly in patients receiving prolonged therapy. Nitrogen dioxide is a byproduct of NO administration and can injure the lung parenchyma; therefore, its concentrations should be maintained below 5 ppm. The initial dose of iNO is usually set at 20 ppm, and reasonable attempts to wean the patient off it should be made every 12–24 hours.

iNO has had an undisputed impact on the management of PHT, and it continues to warrant consideration as adjunctive therapy for some of the more severe patients. However, a recent meta-analysis concluded that iNO does not reduce short-term mortality [96]. It also concluded that there was insufficient information to determine whether it has an impact on neurodevelopmental outcome, long-term mortality and length of hospital stay [96]. iNO is not specifically approved by the US Food and Drug Administration (FDA) for the treatment of post-surgical PHT, although it is approved for the treatment of persistent PHT in term neonates.

Arginine and citrulline are substrates for NO synthase. In addition, arginine, an essential amino acid due to the inability to increase its *de novo* synthesis, plays a central role in cell proliferation, protein synthesis, energy metabolism, and ammonia detoxification, and the question of its relationship with postoperative inflammation and organ dysfunction has been raised. Arginine depletion has been reported after CPB, together with increased expression of arginase, and a fall in both citrulline and glutamine; the mechanism remains uncertain, however, plasma arginine concentrations recovered after day 5 and initiation of enteral feeding [97]. Although the link with NO synthesis has been made, research in the domain of oral arginine or citrulline supplementation has remained inconclusive, with a consequent increase in the plasma concentrations but no impact on the occurrence of PHT postoperatively [98].

Sildenafil

Sildenafil is a selective inhibitor of phosphodiesterase type 5, which increases c-GMP levels in the pulmonary vascular endothelium, as shown in Figure 21.8. When administered orally to healthy subjects, the bioavailability of sildenafil is only approximately 40%. Also, critically ill children may show unpredictable enteral absorption, therefore, i.v. sildenafil may be more appropriate in such cases. Sildenafil is metabolized in the liver, and it has a half-life of about 4 hours. Oral pediatric doses are between 1 and 5 mg/kg, but the greater bioavailability of the i.v. preparations allows effective doses of 0.5 mg/kg.

Sildenafil is at least as effective as iNO for reducing increased PVR in children with CHD [99], and it enhances the pulmonary vasodilator effects of iNO [100]. The use of sildenafil facilitates the successful weaning of patients off iNO [95]. Nevertheless, unlike iNO, because sildenafil is relatively nonselective, systemic administration is associated with a significant increase in intrapulmonary shunting and a clinically nonsignificant fall in arterial blood pressure [99, 100], which may sometimes outweigh its benefits. Intrapulmonary shunting is caused by vasodilatation of the pulmonary arterioles supplying nonventilated areas of the lung, and results in hypoxia.

Although currently approved for use in adults with PHT, sildenafil is extensively used off-label to treat neonates, infants, and children with PHT since 2005. A recent randomized controlled trial of sildenafil for the long-term therapy of children with PHT (STARTS-1) [101], including idiopathic PHT, and PHT associated with connective tissue disease and CHD, demonstrated a decrease in pulmonary artery pressure and PVR with medium and high-dose sildenafil, and no significant change with low-dose sildenafil. However, in the long-term extension study (STARTS-2) [102], there was increased mortality noted at 3 years associated with high-dose sildenafil in children with idiopathic PHT, but not in those with CHD-related PHT. Review of these data by the FDA and European Medicines Agency resulted in contradictory recommendations; sildenafil was approved in Europe in 2011 with a later warning on avoidance of the use of high-dose sildenafil, and the FDA released warnings against the use of sildenafil in pediatric patients aged 1–17 years. In view of the limitations of the START-2 extension study and in view of the Pediatric Pulmonary Hypertension Network consensus, the FDA warning was later revised to add that health care providers should consider the risk and benefits of sildenafil for the individual patient. Tadalafil and vardenafil are two other phosphodiesterase type 5 inhibitors that are currently under investigation.

Prostaglandins

Prostaglandins (PGs) are the main metabolites of the arachidonic acid pathway. They are generated and released by the endothelium, bind to receptors on the underlying arterial smooth muscle, thereby activating adenyl cyclase, increasing c-AMP levels, and inducing smooth muscle relaxation as shown in Figure 21.8. Although PGs are rapidly metabolized by the pulmonary circulation, doses large enough to induce pulmonary vasodilation also induce systemic vasodilation. Inhaled PGs show more selective vasodilator properties than i.v. preparations and, like iNO, they prevent a ventilation/perfusion mismatch by redistributing blood flow to the ventilated aerosol-accessible regions.

PGE_1 was the first PG to be isolated. It is used extensively to maintain the patency of the ductus arteriosus in neonates whose systemic or pulmonary circulation is dependent on ductal patency. In addition, i.v. PGE_1 has been used to treat PHT. Side effects occur in 20–40% of patients treated with higher doses (0.05–0.1 µg/kg/min), but they are reversible upon reverting to a low dose or discontinuing the drug. Nevertheless, the most common side effects, that is, hypotension, apnea, and hyperpyrexia, may complicate the postoperative course and outweigh any potential benefits.

Prostacyclin (PGI_2) was first identified in 1976, and early studies of the use of i.v. PGI_2 in children suggest that it induces highly selective pulmonary vasodilation within the pulmonary vascular bed, where it is inactivated during a single circulation time. However, the efficacy and pulmonary selectivity of the i.v. PGI_2 formulation, epoprostenol, following CHD surgery is similar to that of i.v. PGE_1 [103]. The inhaled formulation, iloprost, also shows good pulmonary selectivity. It also has a longer half-life (25 min), although repeated inhalation is needed for optimum clinical effectiveness. Iloprost may be used as routine therapy of PHT in countries where iNO is not available because of its prohibitive cost [104], since it has been shown to have similar efficacy to iNO in children with CHD [105]. Finally, iloprost may be useful in children who do not respond to iNO therapy or as a rescue therapy when other treatments have failed [104]. Other PGI_2 analogues, such as treprostinil (inhaled), or beraprost (oral) may have potential utility for the treatment of postoperative PHT in children.

Other strategies to improve circulatory function

Corticosteroids

The actions of corticosteroids on the cardiovascular system are mediated via both genomic and nongenomic effects: they exert anti-inflammatory effects by modulating the transcription of RNA and the subsequent synthesis of proinflammatory proteins, and they represent an adjunct therapy that reduces the need for high doses of inotropes by decreasing the reuptake of norepinephrine.

High-dose corticosteroids have strong anti-inflammatory effects and are largely used in the perioperative period [91]. Corticosteroid treatment is associated with lower hyperthermia-related increases in VO_2, reduced fluid requirement, a shorter length of hospital stay [20], and improves myocardial protection [106]. Altogether, modulation of CPB-mediated inflammation by corticosteroids seems clinically beneficial in pediatric patients, especially when targeted to younger and more complex patients. Although the dosing regimen used in children was empirically set at 30 mg/kg prior to CPB, followed by 30 mg/kg at the start of CPB, a recent survey of 36 cardiac surgery centers showed that administration and dosing regimens were mainly based on provider preferences [107].

On the other hand, corticosteroids inhibit norepinephrine uptake by non-neuronal cells, thereby increasing norepinephrine concentration at α-adrenergic receptor sites; additionally, by inhibiting the catechol-O-methyltransferase enzyme, they lead to increases in the plasma norepinephrine concentrations. Corticosteroids also increase cytosolic calcium availability in myocardial and vascular smooth muscle cells and improve capillary integrity in patients with capillary leak syndrome. Finally, they inhibit PGI_2 production and the induction of NO synthase, thereby limiting the pathologic vasodilation associated with the inflammatory response. Corticosteroids can be considered for children with LCOS; however, a formal definition of adequate steroid dosing is required.

Interestingly, the use of low doses (100 mg/m^2/day of a hydrocortisone equivalent) may be sufficient for use as a rescue protocol in children with LCOS [108]. A recent randomized trial in neonates demonstrated that a prophylactic 50 mg/m^2 bolus at the end of CPB, followed by a 50 mg/m^2/day continuous infusion reduced the incidence of LCOS [109]. Therefore, adrenal insufficiency has often been invoked in patients with postoperative LCOS following CPB, which might be similar to what is seen in patients with septic shock, and which can be reversed by the administration of a "substitutive" dosage range. Recent work reported a significant decline in the cortisol response to adrenocorticotropic hormone stimulation throughout the first 24 hours following CPB in infants, associated with increased fluid resuscitation and longer length of stay [110]. Another hypothesis is the suppression of the hypothalamic–pituitary–adrenal axis due to exposure to high-dose perioperative corticosteroids [111], which brings additional arguments against the extensive use of high dosages.

Controversy regarding the perioperative use of corticosteroids is ongoing, and the most recent randomized trials of corticosteroids in neonates with CPB reported no improvement in postoperative outcomes with, however, an improvement in fluid balance and shortening of time to extubation [112–114]. Similar conclusions were drawn from the most recent meta-analysis of the prophylactic use of corticosteroids in CHD surgery [115]. By contrast, a very large study based on data obtained from the Pediatric Heath Information Systems Database, including 46,730 children from 38 US centers from 2003 to 2008, was able to show that the use of corticosteroids was associated with a greater risk of infection, a greater postoperative requirement for insulin, and, finally, longer length of hospital stay (96). The association with morbidity was more prominent in the low-risk group. Similar conclusions were drawn from a subset study restricted to neonates [116].

Thyroid hormone

Thyroid hormone levels are depressed after CPB. Triiodothyroxine (T_3) supplementation has been used in an attempt to increase cardiac index postoperatively with encouraging initial results (99,100): increased cardiac index, decreased inotropic requirement, better fluid balance and shorter time to extubation. Recent meta-analysis of T_3 trials evaluated the impact on clinical outcomes in children and infants with CHD surgery [117, 118]. They reported a very wide variability of dosages, ranging from 0.4 to 5 μg/kg over a 24-hour period, and a wide variation in the duration of therapy, ranging from a single dose at the end of CPB to continued hormone therapy for the duration of intensive care unit (ICU) stay. The inotrope scores were significantly lower in the T_3 group; however, there was no difference in cardiac index, the duration of mechanical ventilation, ICU stay or mortality. No adverse events or delay in the postoperative recovery of thyroid function were reported either.

Beta-adrenergic receptor antagonists

β-adrenergic receptor blockers are beneficial for the management of chronic heart failure in both children and adults because they improve functional status. Patients with chronic heart failure show a downregulation of β-adrenergic receptors due to increased sympathetic tone; β-blockers, such as propranolol, metoprolol, and carvedilol increase the number of myocardial β-adrenergic receptors and improve myocardial function.

In the acute setting of CHD surgeries, β-blockers reduce the effects of increased sympathetic tone on the RV infundibulum and heart rate in patients with tetralogy of Fallot, thereby improving RV filling. Esmolol, a short-acting β_1-receptor selective antagonist, is well suited for the perioperatively treatment of tetralogy of Fallot patients [119]. Esmolol (100–700 μg/kg/min) controls postoperative hypertension following coarctation repair [120] and avoids reflex tachycardia that results from the use of selective vasodilators.

Calcium

Administration of calcium in the form of calcium chloride or calcium gluconate helps improve the inotropic function of the heart in patients with hypocalcemia. This is especially important in neonates, in whom plasma membrane Na–Ca

exchange and calcium influx channels play a greater role than the sarcoplasmic reticulum in regulating intracellular calcium concentrations; therefore, neonates are highly dependent on extracellular calcium. Neonates receive significant amounts of citrated blood products; however, citrate binds calcium and causes hypocalcemia. Calcium is also a major role in excitation–contraction coupling in smooth muscle, and functions as a vasoconstrictor.

However, routine administration of calcium salts upon termination of CPB is a subject of debate. Elevated intracellular calcium levels are associated with injury and cell death during ischemia and reperfusion [121]. This is further aggravated in the neonatal myocardium, where the sarcoplasmic reticulum is underdeveloped and does not insure calcium uptake in the case of an elevation in intracellular calcium levels.

Sodium bicarbonate

Buffering acidosis is essential in patients with, or at risk of, high PVR. The deleterious effect of acidosis on PVR, particularly in hypoxemic conditions, was demonstrated experimentally more than 50 years ago [122], and the patterns of PVR variations as a response to changes in pH are shown in Figure 21.9. More recently, it has been shown that the administration of sodium bicarbonate to increase pH in infants with increased PVR reduces PVR by approximately 50% and increases cardiac index by approximately 35%, even if hypercapnia is present [123]. This agrees with a previous study showing that pH plays a major role in regulating PVR, and that metabolic alkalosis is as effective as respiratory alkalosis for treating hypoxia-induced pulmonary vasoconstriction [124].

Lactic acid levels increase due to cellular hypoxia, and lactic acidosis is an adaptive mechanism that enables an organism to survive hypoxic conditions. Lactic acidosis moves the dissociation curve for hemoglobin to the right, thereby allowing improved oxygen transfer to the tissues. Therefore, while extreme values of acidemia (pH < 7.2) interfere with myocardial performance and responses to catecholamines, and should be buffered, a pH lower than normal is essential for adaptation. Bicarbonate buffering has several side effects, including paradoxical intracellular acidosis and further impairment of cardiac function [125], a risk of hypernatremia, the creation of a hyperosmolar state, and a risk of intraventricular hemorrhage in neonates.

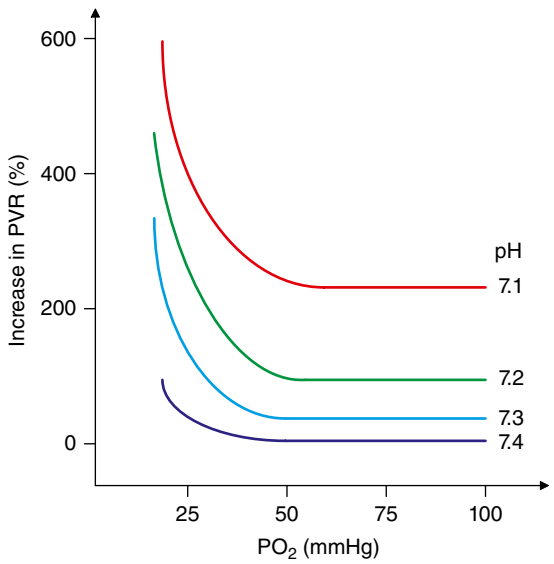


Figure 21.9 Patterns of pulmonary vascular responses to changes in pH and PO_2. (Source: Rudolph & Yuan [122]. Reproduced with permission of The American Society for Clinical Investigation.)

Isoproterenol

Isoproterenol, a nonselective β-adrenergic receptor agonist, is a synthetic derivative of norepinephrine. Isoproterenol has more chronotropic than inotropic effects and lowers the SVR. It is used to treat hemodynamically significant bradycardia and during cardiac anesthesia in the denervated heart immediately after transplantation. High doses of isoproterenol can be arrhythmogenic, and it is often used in electrophysiologic studies. Isoproterenol induces an increase in myocardial VO_2, whereas DO_2 decreases as a result of reduced coronary diastolic filling; this may exacerbate or induce ischemia. Therefore, patients receiving isoproterenol should be volume replete.

Fenoldopam

Fenoldopam is a selective D_1-receptor agonist that shows potent vasodilatory effects, particularly in the renal, mesenteric, coronary, and skeletal muscle vascular beds. Fenoldopam maintains adequate renal perfusion while reducing blood pressure at the same time. Few data are available regarding its use following CHD surgery. Small, albeit randomized, studies show that it is safe in neonates and has a beneficial effect on kidney function following CPB when high doses are used (1 μg/kg/min) [126, 127].

Current practices

Two recent surveys describe the current international practice variation: the EuLoCOS-Ped European survey [27, 32], completed in 2009, collecting information from 90 centers from 31 European countries, and the survey of the Pediatric Cardiac Intensive Care Society (PCICS) [26], completed in 2015, reporting practices in 62 centers, 69% of whom were North American. Medical treatment of LCOS is constrained by a lack of appropriate drug and dosing guidance as acknowledged by the respondents of the European survey [27, 32]. Overall, the EuLoCOS survey alone reports 24 different drug regimens to prevent LCOS, and 39 drug regimens to treat LCOS [27, 32]. Besides, as mentioned before, 78% of all patients receive at least one cardiovascular drug off-label, with surgical CHD patients receiving a median of three drugs off-label [28]. Dobutamine alone is licensed for use as inotropic support in children with LCOS in Spain and Germany [128], although, efficacy data are lacking in neonates.

Preventive LCOS therapy is a common practice, reported in 77.8% of all pediatric cases in the EuLoCOS survey. However, there is a large variability in the choice of drugs being used, as shown in Table 21.4. The distribution of the timing of administration is different as well. In 64%

Table 21.4 Current practices for the management of low cardiac output syndrome after congenital heart surgery

EuLoCOS survey				PCICS survey	
LCOS prophylactic drug regimen			**%**	**LCOS prophylactic drug regimen**	**%**
Milrinone			25	Milrinone	97
Milrinone + dopamine			12	Epinephrine	45
Milrinone + epinephrine			11	Dopamine	38
Milrinone + dobutamine			9	Dobutamine	11
Milrinone + levosimendan			7	Levosimendan	5
Levosimendan			7		
Timing of administration			**%**	**Timing of administration**	**%**
Intra- and postoperatively			57	Preoperatively	1
Pre-, intra-, and postoperatively			21	After anesthetic induction	1
Intraoperatively			8	When on CPB	42
Postoperatively			8	While coming off CPB	63
Preoperatively			4	In the Intensive Care Unit	29
Pre- and intraoperatively			1		
Treatment of LCOS with elevated SVR	**%**	**Treatment of LCOS with elevated PVR**	**%**	**Treatment of LCOS**	**%**
Initial treatment		Initial treatment		First choice	
• Milrinone	34	• Milrinone	17	• Milrinone	42
• Milrinone + dobutamine	8	• iNO + milrinone	13	• Epinephrine	36
• Milrinone + dopamine	8	• iNO	10	• Dopamine	15
First add-on		First add-on		• Dobutamine	2
• Epinephrine	24	• iNO	20	Second choice	
• Milrinone	11	• Epinephrine	11	• Epinephrine	39
• Nitroprusside	9	• Sildenafil	11	• Milrinone	15
Second add-on		Second add-on		• Corticosteroids	10
• Epinephrine	22	• Prostacyclin derivatives	22	• Dopamine	9
• Levosimendan	22	• iNO	14		
• Dobutamine	12	• Sildenafil	14		

LCOS: low cardiac output syndrome, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance
Results from the EuLoCOS survey 2009 (left) [27, 32] and from the Pediatric Cardiac Intensive Care Society (PCICS) survey 2015 (right) [26].

of all cases, milrinone in prophylactically administered in European centers to prevent LCOS, however, the dosage and duration of administration differ substantially among hospitals: the bolus dose varies from 20 to 300 µg/kg, the maintenance infusion ranges from 0.2 to 1 µg/kg/min, and the duration varies between 6 and 168 hours. The dose of milrinone appears to be less than that recommended by PRIMACORP [4], which may be due to concerns about the potential side effects, particularly hypotension and age-specific pharmacokinetic differences in drug elimination [51]. In 32% of cases, milrinone is associated with a catecholamine in the EuLoCOS survey: dopamine, dobutamine, epinephrine, and levosimendan are used in about 16% of cases each, with a large variety of dosages. Of the PCICS respondents, 97% use milrinone to prevent LCOS, most of the time in association with a catecholamine: epinephrine in 43%, dopamine in 36%, dobutamine in 11% and levosimendan in 11% of cases. The high percentage of centers using catecholamines as a preventive therapy, 32% in EuLoCOS and 94% in the PCICS survey, is surprising in view of their serious side effects mentioned before.

The therapeutic strategies to treat LCOS, such as reported by the EuLoCOS and PCICS surveys, are shown in Table 21.4. In keeping with the European survey [32], the six drugs that constitute 90% of total drug use to treat LCOS in children are milrinone, dopamine, dobutamine, epinephrine, levosimendan, and methylprednisolone. Milrinone monotherapy was the preferred drug regimen for the initial treatment of LCOS with elevated SVR, epinephrine was the preferred first add-on drug and levosimendan was added as the next step. Milrinone monotherapy was the treatment of choice for the initial treatment of LCOS with elevated PVR, the first and second add-on drugs were iNO and PGI_2 derivatives. The PCICS survey revealed milrinone being used as a first choice in only 42% of cases with LCOS, whereas catecholamines (epinephrine and dopamine) were used in 51% of cases. This, again, is surprising in the context of postcardiac surgery LCOS, where the major therapeutic objectives are the decrease of LV and RV afterload, and avoidance of myocardial oxygen debt.

Inotropic and vasoactive scores

Inotropic and vasoactive scores are derived from summing the maximum dose rates, using correction factors to account for differential units of measurement of inotropes and vasopressor medications administered in the first 24 hours after cardiac surgery. The inotropic score (IS) was first proposed in the Boston Circulatory Arrest Study [3] to quantify the pharmacologic cardiovascular support given postoperatively. Later on, it has

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often been used as a measure of illness severity following cardiac surgery in children even though the score was not created for this purpose. Gaies et al. [129] proposed expanding the IS to include other commonly used vasoactive medications, such as milrinone, vasopressin, and norepinephrine, and called it the vasoactive-inotrope score (VIS). The scores are calculated as:

$$\begin{aligned} \text{IS} = {} & \text{Dopamine dose}\,(\mu\text{g/kg/min}) \\ & + \text{Dobutamine dose}\,(\mu\text{g/kg/min}) \\ & + 100 \times \text{Epinephrine dose}\,(\mu\text{g/kg/min}) \end{aligned} \tag{21.17}$$

$$\begin{aligned} \text{VIS} = {} & \text{IS} + 10 \times \text{Milrinone dose}\,(\mu\text{g/kg/min}) \\ & + 10{,}000 \times \text{Vasopressin dose}\,(\text{units/kg/min}) \\ & + 100 \times \text{Norepinephrine dose}\,(\mu\text{g/kg/min}) \end{aligned} \tag{21.18}$$

In the absence of a specific pediatric cardiac scoring system for the prediction of postoperative outcome, the VIS has been adopted by many centers as an estimator of the severity of critical illness. A multicenter analysis of data reported to the Pediatric Cardiac Critical Care Consortium [130] showed that the maximum VIS calculated in the first 24 hours after cardiac intensive care unit (CICU) admission was strongly and significantly associated with morbidity and mortality, and a maximum VIS $\geq$ 20 predicted an increased likelihood of clinical outcomes, such as mechanical circulatory support, cardiac arrest, renal replacement therapy, neurologic injury, or mortality. Furthermore, when comparing the predictive ability of LCOS, as defined by clinical parameters, and of the VIS for postoperative outcomes, it appeared that clinically derived LCOS was not associated with early postoperative outcomes, whereas the VIS was correlated with durations of mechanical ventilation, ICU stay, and total hospital charges [19]. Our inability to diagnose LCOS based on clinically available parameters alone is acknowledged [131], therefore, the VIS has the opportunity to be considered for inclusion into scoring systems as a metrics or diagnostic criterion to improve current definitions of LCOS.

Individualized perioperative hemodynamic management

In the large majority of cases, children undergo biventricular repair and develop variable degrees of myocardial stunning due to CPB-related injury. Most often, they require either a so-called "hands-off" approach, with minimal intervention and careful observation, or a gentle inodilation therapy. However, the ideal therapeutic approach for one type of circulatory physiology may be detrimental in another, therefore, it is difficult to provide general guidelines for hemodynamic management. An excellent educational review published by Shekerdemian in 2009 [132] highlights the need for an individualized strategy, based on a sound knowledge of the underlying physiologies. Examples of individualized hemodynamic management strategies are shown in Table 21.5.

Abnormalities of diastolic function following right heart surgery. After repair of tetralogy of Fallot, an LCOS is seen in nearly 50% of patients, as a result of RV diastolic failure [24]. This is most likely the result of the exposure of the hypertrophied RV to CPB and reperfusion injury. RV function may further alter due to right ventriculostomy, and especially when the incision is extended across the pulmonary annulus. Transannular patches result in massive pulmonary regurgitation and RV volume overload. In addition, if the pulmonary arteries are hypoplastic, than the RV afterload is increased too. Finally, there is invariably some degree of right bundle branch block after surgery, causing ventricular asynchrony.

Because systolic function is intact, inotropic agents are of little benefit. LCOS results from inadequate RV filling, which is compounded by a reduction in the effective compliance of the LV. During diastole, the hypertensive RV alters the normal trans-septal pressure gradient, causing the ventricular septum to bow into the LV [24]. Spontaneous ventilation, or negative pressure ventilation if the patient's clinical status does not allow extubation, have been shown to improve hemodynamics [133, 134]. Fluid administration is of some benefit; however, the benefit is limited because volume load increases the RV end-diastolic pressure and volume, and rapidly results in RV dilation, tricuspid regurgitation and further decrease in RV output. Therefore, fluid administration should be careful and rapidly relayed by low-dose vasoconstrictors.

Early palliation for functionally univentricular circulation. In infants with a functionally univentricular heart, the total CO is distributed from a single ventricular stroke volume to the systemic and pulmonary circulations, and the relative distribution of flow is dictated by their respective vascular resistances. In these patients, it is usually necessary to maintain a well dilated systemic vasculature, while controlling the PVR.

Using computer simulations to study the single-ventricular circulation, Barnea et al. [9] demonstrated that high values of Q_P/Q_S are always associated with low DO_2, which is only partially compensated by increases in CO. Ideally, Q_P/Q_S should be kept below 1.5, and a Q_P/Q_S ratio between 0.8 and 1.2 with a $SvO_2 > 50\%$ have become the targets of postoperative managements following the Norwood procedure [81]. Li et al. [5] demonstrated that the largest amount of DO_2 variability is due to Q_S and RVS, and vasodilation of the systemic circulation is acknowledged as a major contributor to the improvement of DO_2. Manipulations of the pulmonary circulation have only minor effects [5]. Accordingly, Hoffman et al. [81] demonstrated that the most effective approach to improve the inefficiency of the single-ventricle circulation is to alter the intense sympathetically mediated systemic vasoconstriction using potent α-adrenergic receptor blockers, such as phenoxybenzamine.

Following the Norwood procedure with a systemic-to-pulmonary anastomosis for hypoplastic left heart syndrome, the neonate has a unique convergence of several physiologic vulnerabilities: myocardial dysfunction following ischemia, reperfusion, and CPB, potential limitations of a morphologically right single ventricle and potential aorto-coronary flow limitation. Because of the risk of additional myocardial ischemia due to a drop in diastolic arterial pressure, excessive systemic vasodilation and hypotension should be avoided and/or treated. The Sano modification has proven to increase very short-term survival by improving the coronary perfusion of the single ventricle [135]; however, long-term results did not improve.

Table 21.5 Examples of individualized postoperative hemodynamic management

Underlying physiology	Hemodynamic considerations	Target effect	Current recommendations
Biventricular circulation early after CPB	Increased afterload ± Myocardial dysfunction	None Vasodilation or inodilation Gentle inotropic stimulation	None Milrinone Low-dose epinephrine or dobutamine
Severe systolic dysfunction	Myocardial dysfunction Increased afterload	Increased inotropy Vasodilation	Low-dose epinephrine or dobutamine Milrinone Levosimendan Consider CPS
Diastolic dysfunction	Good systolic function Hypertrophied and noncompliant ventricle	Preload increase Slight vasoconstriction	None Careful fluid administration Low-dose norepinephrine
Univentricular circulation, early palliation	Q_P/Q_S ratio dictated by their respective vascular resistances	Favor Q_S through afterload reduction Gentle inotropic stimulation if needed	Phenoxybenzamine Dobutamine or low-dose epinephrine Milrinone
Systemic-to-pulmonary artery anastomosis	Systolic function is usually good Myocardial ischemia due to diastolic runoff	Inodilation to increase systemic perfusion Minimal vasoconstriction to maintain diastolic perfusion pressure Stable PVR	Low-dose epinephrine Norepinephrine
Postop. Fontan	Systolic function is usually good Passive pulmonary blood flow	Pulmonary vasodilation	Oxygen, iNO Milrinone
Postop. bidirectional cavopulmonary anastomosis	Systolic function is good Pulmonary blood flow is passive and equals SVC flow	Pulmonary vasodilation has little effect	None
Residual outflow tract obstruction	Good systolic function	Preload increase Vasoconstriction	Careful fluid administration Norepinephrine

CPB: cardiopulmonary bypass, CPS: cardiopulmonary support; iNO: inhaled nitric oxide; PVR : pulmonary vascular resistance; Q_P/Q_S: Pulmonary blood flow / systemic blood flow ratio, SVC = superior vena cava
(Source: Adapted from Shekerdemian [132].)

Fontan operations and bidirectional cavopulmonary (Glenn) anastomosis. LCOS is the main cause of morbidity and mortality in this group. After the Fontan operation, Q_P is a passive diastolic flow, extremely sensitive to changes in intrathoracic pressure. Therefore, the key to optimising CO often lies in achieving early extubation, as advocated by Fontan himself. Besides, oxygenation is significantly improved by pulmonary vasodilators, which facilitate passive flow into the pulmonary arteries and increase Q_P. When given in hypoxic patients after Fontan operations, iNO lowers transpulmonary gradient by 40–50% and decreases central venous pressure by 15–20% [93]. In such situations, the addition of 0.5 µg/kg/min of milrinone to the regimen results in a synergistic effect, with a further fall in the transpulmonary gradient and a significant improvement in the oxygenation indices [136]. Other factors may alter oxygenation, and are less susceptible to medical therapy: pulmonary venous admixture, systemic venous collaterals, and pulmonary arterio-venous malformations.

As in the case of Fontan circulation, the pulmonary flow following a Glenn anastomosis is passive diastolic and sensitive to changes in the intrathoracic pressure, and keep the upper body elevated, as well as early extubation are key strategies to optimize CO. As shown in equation (21.15), following the Glenn anastomosis DO_2 is a complex function of CO and Q_{SVC}/Q_{IVC} ratio, where Q_{SVC} equals Q_P. Thus, cerebral and pulmonary circulations are connected exclusively in series with each other, and the cerebral and pulmonary autoregulatory mechanisms are in direct competition with each other. There are limited pharmacological options to increase Q_P in this situation, and oxygen or pulmonary vasodilators have only marginal effect; because cerebral autoregulatory feedback loops override the pulmonary ones, the main factor to increase cerebral blood flow, and as a consequence Q_P and global CO, is hypercarbia [137]. This will be discussed in detail later on.

Residual obstruction to systemic or pulmonary outflow. In a minority of children, an LCOS can be directly attributable to residual anatomic lesions. They do not generally respond to medical treatment, and most often require invasive intervention.

In case of significant residual obstruction of the systemic outflow, as seen after relief of aortic stenosis, or after double outlet right ventricle repair, or of the pulmonary outflow, as seen after tetralogy of Fallot repair, reoperation is needed in order to fully relieve the obstruction. However, until this is achieved, a reduction of the preload or afterload with vasodilators is generally not desirable, as it may result in an acute

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fall in cardiac output. An active inotrope-oriented strategy is not desirable either, since inotropes may increase the outflow obstruction, and the best strategy is to maintain ventricular preload plus low-dose vasoconstrictors.

KEY POINTS: IMPROVING POSTOPERATIVE OXYGEN TRANSPORT BALANCE

- Inodilators are the most effective and the most commonly used drugs in the setting of CHD surgery, both for the prevention and treatment of LCOS.
- Milrinone and epinephrine are the preferred drugs; however, levosimendan has desirable properties and is a promising alternative.
- Catecholamines have significant metabolic side effects, increase myocardial VO_2, and may have variable effects in CHD patients due to variability in receptor function.
- The pharmacological agents used to improve oxygen transport balance should be chosen based on the underlying pathophysiology.

Cardiopulmonary interactions

Mechanical ventilation plays a crucial role in the hemodynamic management of patients following CHD surgery [138]. It is easy to underestimate the effects of ventilation on the cardiovascular system or to misinterpret cardiopulmonary interactions as primary cardiovascular events. Both spontaneous and mechanical ventilation induce changes in intrapleural, intrathoracic pressure, and in lung volume, which can independently affect the key determinants of cardiovascular performance. In 1948, Cournand et al. [139] showed that CO was reduced in patients receiving intermittent positive pressure ventilation via a mask. This study, one of the first to investigate cardiopulmonary dynamics during mechanical ventilation, showed that CO was inversely correlated with RV filling pressure, which was, in turn, directly influenced by the ventilator settings.

A reduction of FRC after anesthesia and thoracic surgery may cause atelectasis, hypoxia, and respiratory failure. CPB and reperfusion injury result in an intense general inflammatory reaction and diffuse endothelial damage with an increase in vascular permeability. Alveolar and interstitial edema, which may or may not be clinically apparent, reduces dynamic lung compliance (the ratio of the tidal volume to peak inspiratory pressure) and increases the ventilation/perfusion mismatch [138]. Mechanical ventilation reverses the inevitable reduction in FRC caused by anesthesia and thoracic surgery, but high mean airway pressures may be necessary to provide equivalent gas exchange in less compliant lungs. This can result in a decrease in CO. Four decades ago, Jenkins et al. [140] demonstrated the cardiopulmonary effects of stopping mechanical ventilation after open-heart surgery in 17 children: FRC, pH, and PaO_2 were significantly reduced, whereas RV stroke index significantly increased. The mean FRC on spontaneous ventilation was below normal levels, despite continuous positive airway pressure, and there was a significant increase in PVR in patients with an FRC that fell below 22 mL/kg while on spontaneous ventilation.

Effects of changes in intrathoracic pressure

Effects of changes in intrathoracic pressure on the left heart

The aortic transmural pressure (aortic pressure–intrathoracic pressure) increases during spontaneous inspiration, due to the fall in pleural pressure. As such, the afterload of the LV increases, which may cause pulmonary edema in patients with poor LV function when weaning from mechanical ventilation. Conversely, positive pressure ventilation decreases the afterload of the LV by decreasing the transmural pressure of the LV, and improves VO_2/DO_2 indirectly, by reducing the work of breathing and the negative inspiratory swings in intrathoracic pressure. LV failure and pulmonary edema are also associated with an increased intrathoracic blood volume. By limiting venous return, a positive intrathoracic pressure, or even simply the use of positive end-expiratory pressure, can improve the hemodynamic.

Effect of changes in intrathoracic pressure on the right heart

In the absence of a left-to-right shunt, the CO is equivalent to the systemic venous return. The systemic venous return depends on the pressure gradient between the extrathoracic veins and the RA pressure. Spontaneous inspiration induces a negative intrapleural pressure and increases the RA transmural pressure (RA pressure–intrathoracic pressure). As a result, the RA increases in size and the RA pressure falls. This favors venous return and increases RA filling. Conversely, during positive pressure inspiration, the RA transmural pressure decreases, the size of the RA decreases and the RA pressure increases, thereby lowering the gradient for venous return, and causing it to decelerate. This phenomenon is aggravated in case of hypovolemia and of gas trapping associated with obstructive airway disease. Circulatory reflexes (adrenergic-mediated reductions in venous capacitance and renin-angiotensin-aldosterone system induced volume expansion) increase the circulatory filling pressure in an attempt to maintain the pressure gradient for venous return. Volume loading and ventilatory strategies to reduce the intrathoracic pressure can be used to compensate and augment venous return.

Effects of changes in intrathoracic pressure on PVR

PVR is the main determinant of RV afterload and is directly affected by changes in lung volume. PVR depends on the balance between the vascular tone of the alveolar vessels, and that of the extra-alveolar or parenchymal vessels. PVR can increase at either extreme of lung volume, as shown in Figure 21.10 [138]. When the lung is inflated above the FRC, the alveolar vessels become compressed due to alveolar distension. As the lung volume falls towards the residual volume, the terminal airways collapse, which in turn causes alveolar collapse; this ultimately results in hypoxic pulmonary vasoconstriction. When ventilating near "normal FRC," the impact on PVR and RV afterload is minimal.

High-frequency oscillatory ventilation allows lung volume to be maintained near FRC and avoids the detrimental effects of large wings in lung volume on PVR.

Delayed sternal closure

Leaving the sternum open causes a substantial increase in the total respiratory system compliance. Pericardial and sternal closures produce constrictive effects and may interfere with efficient mechanical ventilation after cardiac operations. This is important for infants in whom considerable capillary leak and edema may develop after CPB, and in whom cardiopulmonary interactions have a significant impact on immediate postoperative recovery. Delayed closure is also used electively in high-risk neonates, as a means of maintaining hemodynamic and respiratory stability during the initial postoperative period [141]. Delayed sternal closure is not associated with an increased risk of surgical site infections. Significant hemodynamic changes are seen at the time of sternal closure: atrial pressure and heart rate increase, and mechanical ventilation requirements increase as a result of reductions in total respiratory system compliance, tidal volume, and expired CO_2, as shown in Figure 21.11 [142]. Significant increases in the fraction of inspired oxygen, peak inspiratory pressure and ventilatory rate may be required to maintain tidal volume and gas exchange. After a sustained negative fluid balance is achieved, the sternum can be successfully closed within a couple of days; a retrospective study performed at a large tertiary care center suggested a mean of 3–4 days [141].

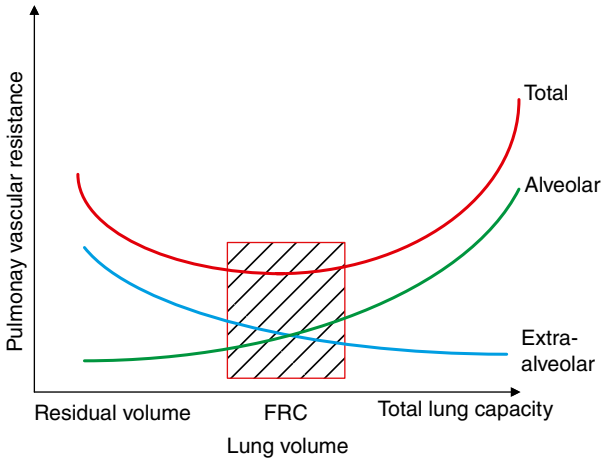


Figure 21.10 Schematic representation of the relation between lung volume and the pulmonary vascular resistance. (Source: Shekerdemian & Bohn [138].)

Individualized management of the ventilation parameters and cardiopulmonary interactions

As with cardiovascular drugs, appropriate ventilation for one child may be unsuitable for another, depending on the underlying physiology and circulatory status. An illustration of the variability in the ventilation targets according to the underlying pathology is shown in Table 21.6.

Systolic LV dysfunction. Patients with systolic LV dysfunction benefit from positive pressure ventilation. This is particularly so in infants with transposition of the great arteries and an intact ventricular septum being operated late after birth, and in those after repair of the anomalous left coronary

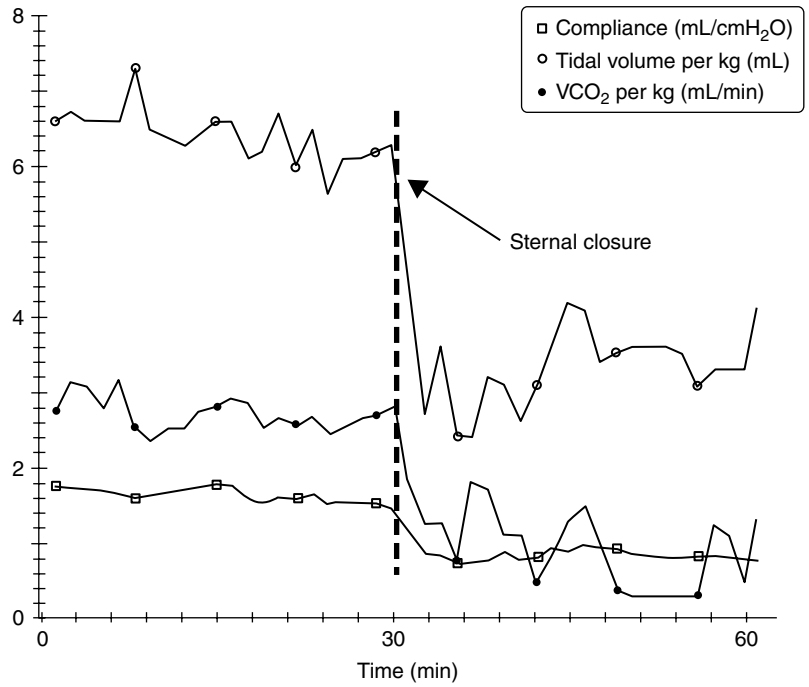


Figure 21.11 Sixty-minute trend in recorded data during sternal closure in a 2-week-old (3.3 kg) infant. (Source: Main et al. [142]. Reproduced with permission of Wolters Kluwer Health, Inc.)

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Table 21.6 Examples of individualized postoperative management of cardiopulmonary interactions

Underlying physiology	Spontaneous respiration	Positive pressure ventilation	Guide for routine ventilation
Systolic dysfunction early after CPB	Negative intrapleural pressure increases LV afterload	Reduced work of breathing Reduces LV afterload and RV preload through avoiding negative swing in pleural pressure	Positive pressure ventilation is beneficial Consider extubating to CPAP
Tetralogy of Fallot with restrictive RV	Negative intrapleural pressure increases RV preload and diastolic pulmonary artery flow	Reduced RV preload and diastolic pulmonary artery flow	Low airway pressures early after surgery Early extubation
Postop. Fontan	Negative intrapleural pressure improves pulmonary flow, which is passive	Reduced preload and pulmonary flow	Low airway pressures early after surgery Early extubation
Postop. bidirectional cavopulmonary anastomosis	Negative intrapleural pressure improves pulmonary flow, which is passive	Reduced pulmonary flow Increased cavopulmonary pressures	Keep upper body elevated Mild respiratory acidosis while ventilated Early extubation
Systemic-to-pulmonary artery anastomosis	Preoperative tachypnea may result in respiratory alkalosis, pulmonary overcirculation and systemic hypoperfusion	Enables pre- and postoperative control of the pulmonary flow	Stable PVR, maintain normal $PaCO_2$ and pH Little role for hypoxic gas mix

CPAP: continuous positive airway pressure; CPB: cardiopulmonary bypass, LV: left ventricle; $PaCO_2$: partial arterial carbon dioxide tension; RV: right ventricle
(Source: Adapted from Shekerdemian [132].)

artery from the pulmonary artery. Elective continuous positive airway pressure ventilation should be considered routinely after tracheal extubation.

Diastolic RV dysfunction and Fontan circulation. Patients with RV diastolic impairment have responses to positive pressure ventilation, which are very different from those with systolic dysfunction. Isolated RV diastolic dysfunction is seen in nearly 50% of patients with a tetralogy of Fallot repair [24] and can result in LCOS due to impediment of the pulmonary blood flow. If the patient's clinical status allows, a method of ventilation that permits patient-initiated breathing will result in a lower intrathoracic pressure than if all breaths are ventilator derived. It is also suggested that negative pressure ventilation, which increases pulmonary blood flow by up to 67% in patients suffering from RV diastolic dysfunction, might be a useful hemodynamic tool in such cases [134]. Postoperative care should include the use of conservative airway pressure aiming for early extubation.

A very similar situation is seen in patients following the Fontan operation. Pulmonary blood flow in the Fontan circulation is predominantly passive, and depends on adequate venous return to a low resistance, unobstructed pulmonary circulation. The pulmonary blood flow is very dependent on a low intrathoracic pressure, and augmented by a negative intrathoracic pressure, such as seen during spontaneous respiration. During positive pressure ventilation, the pulmonary blood flow is compromised, and therefore, early extubation is often the key to optimizing CO. Negative pressure ventilation has been tried in Fontan patients with an LCOS in whom early extubation was not possible: pulmonary blood flow increased by 42% and CO improved by an increase in stroke volume [143].

Bidirectional cavopulmonary (Glenn) anastomosis. There are similarities between the pulmonary circulation of patients after bidirectional cavopulmonary anastomosis and those with the Fontan circulation, in that the Q_P is preload-dependent and relies upon a low resistance and unobstructed pulmonary bed. Similar to Fontan patients, they should be ventilated with conservative airway pressures, aiming early extubation. A consequence of circulation following Glenn anastomosis is that cerebral and pulmonary circulations are connected exclusively in series with each other. Thus, the cerebral and pulmonary autoregulatory mechanisms are in direct competition with each other: the brain vasculature dilates in response to hypercarbia, and the lung vasculature vasoconstricts, and the opposite holds true for hyperoxia [144]. The result is that the cerebral autoregulatory feedback loops override the pulmonary one, and hypercarbia markedly increases cerebral blood flow, and as a consequence Q_P, oxygenation indices and the global CO. A prospective observational study in infants undergoing the Glenn anastomosis showed that when increasing $PaCO_2$ from 35 to 45 and 55 mmHg, cerebral blood flow and Q_P increased, as did CO. It was also suggested that the effect of CO_2 on global oxygenation was not the result of selective cerebral vasodilatation, but rather a consequence of an increase in Q_S and decrease in SVR [137]. Both oxygen and iNO, which are potent pulmonary vasodilators, have little impact [145], and hyperventilation with alkalosis does not improve systemic oxygenation after the Glenn anastomosis [146].

Postoperative PHT. Postoperative PHT may complicate the recovery of infants after repair of obstructed pulmonary venous drainage, or after closure of large left-to-right shunts. Ventilatory targets should include low/normal $PaCO_2$, the absolute avoidance of hypoxia and of agitation or stress, and

sedation boluses should be routinely considered before endotracheal suction in high-risk patients.

Systemic-to-pulmonary artery anastomosis. In patients with hypoplastic left heart syndrome before or after a systemic-to-pulmonary artery anastomosis, ventilation was used to induce pulmonary vasoconstriction through deliberate acidosis and hypoxia, with the intention of decreasing pulmonary perfusion and increasing systemic perfusion. This, however, is now questioned, since it has been shown that the main driver of an improvement in systemic DO_2 is systemic vasodilation; modest additional inspired oxygen, a normal $PaCO_2$, and a normal acid–base balance result in further improvement of the systemic DO_2 [5].

KEY POINTS: CARDIOPULMONARY INTERACTIONS

- PPV can compromise RV function by decreasing venous return (preload).
- PPV can improve LV function by decreasing ventricular transmural pressure gradient (afterload).
- PPV near normal FRC has the least effect on PVR.
- Sternal closure exacerbates cardiopulmonary interactions.
- The management of cardiopulmonary interactions depends on the pathophysiology of the underlying CHD.

Monitoring

Estimating the adequacy of DO_2 in pediatric patients with CHD is challenging. In addition to findings on physical examination, parameters derived from electronic monitoring have become a major quantitative description of patient state. There are no specific recommendations for the monitoring following pediatric cardiac surgery. The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) has established recommendations for the monitoring of critically ill children based upon expert consensus [147]. There is a strong agreement upon the fact that there is no single clinical parameter that allows evaluation of the global hemodynamic status in children, and that hemodynamic therapy should not be titrated solely based on clinical signs. The periodical evaluation and serial longitudinal assessment of clinical and hemodynamic monitoring parameters is also strongly recommended, in order to assess response to therapy.

Clinical hemodynamic variables and standard perioperative monitoring

Although clinical hemodynamic variables, such as heart rate, capillary refill, core peripheral temperature gap and fluid balance are the mainstay of critical care management in CHD patients, they are poor predictors of adverse outcomes. Standard and routinely perioperative monitoring parameters include invasive blood pressure, central venous pressure, pulse oximetry, and continuous capnography in intubated patients.

Invasive blood pressure monitoring is indicated during cardiac surgery with CPB. Although it does not provide direct information about CO, evidence point to the utility of the quantification of respiratory variation in blood pressure as an indicator of preload responsiveness [148]. Central venous pressure is commonly placed for the perioperative period of CHD surgery, and it is thought to be a surrogate for RV preload, although sensitive to ventricular compliance. Many centers additionally monitor left atrial pressure through a left atrial line placed intraoperatively. It is an indicator of the LV preload, although the relationship between left atrial pressure and LV preload varies with changes in LV compliance, which are common following CPB. Left atrial lines are mostly used in neonates, in patients with hypoplasia and/or outflow obstruction of the LV, and in those with mitral surgeries; they also allow for the calculation of the transpulmonary gradient in patients who undergo staged single-ventricle palliation.

Pulse oximetry is a standard of care in pediatric anesthesia since the 1990s, and has greatly reduced the incidence of perioperative hypoxic injury. There are, nevertheless, important sources of error inherent to pulse oximetry, such as movement, dyshemoglobinemia, tissue pigment, and LCOS; it is acknowledged that it tends to overestimate arterial saturation as the arterial saturation decreases.

Capnography, an indicator of $PaCO_2$, identifies endotracheal tube displacement, airway obstruction, and is an indicator of pulmonary perfusion during resuscitation. However, the end-tidal PCO_2–$PaCO_2$ gradient widens with a reduction in pulmonary blood flow, such as seen in LCOS, obstruction to pulmonary blood flow or pulmonary hypertensive crisis.

Despite of their widespread adoption, none of these parameters quantifies DO_2, and the identification of inadequate DO_2 before hypoxic–ischemic insult occurs relies on the ability of the clinician to interpret these parameters. Such a limitation can be illustrated by taking the postoperative period following the Norwood operation as an example. Using simulations of the single-ventricle circulation, Barnea et al. [9] demonstrated a nonlinear relationship between DO_2 and SaO_2 (Figure 21.12, panel A). As SaO_2 increases, DO_2 increases, reaches a peak, and then decreases rapidly. Peak DO_2 occurs at $Q_P/Q_S < 1$. However, following the Norwood operation, Q_P/Q_S is commonly about 1.5. When $Q_P/Q_S > 1$, slight increases in SaO_2 are associated with large decreases in DO_2.

Another illustration of these limitations is fluid balance, another commonly monitored clinical parameter. A positive fluid balance has a detrimental impact on organ function in critically ill children, as shown by the dose–response relationship between increasing degrees of fluid overload and the length of mechanical ventilation and PICU stay [149]. However, factors, such as bleeding and hypovolemia, use of perioperative ultrafiltration, use of diuretics, and postoperative acute kidney failure can bias fluid balance in the setting of CHD surgery. On the other hand, the most critically ill patients require more initial fluid resuscitation; thus, it is unclear whether fluid balance is simply the result of the severity of illness or is an independent contributor to multiorgan dysfunction. Furthermore, the most important challenge is likely to be the assessment of acute fluid redistribution which is a consequence of the inflammatory response to CPB, variable

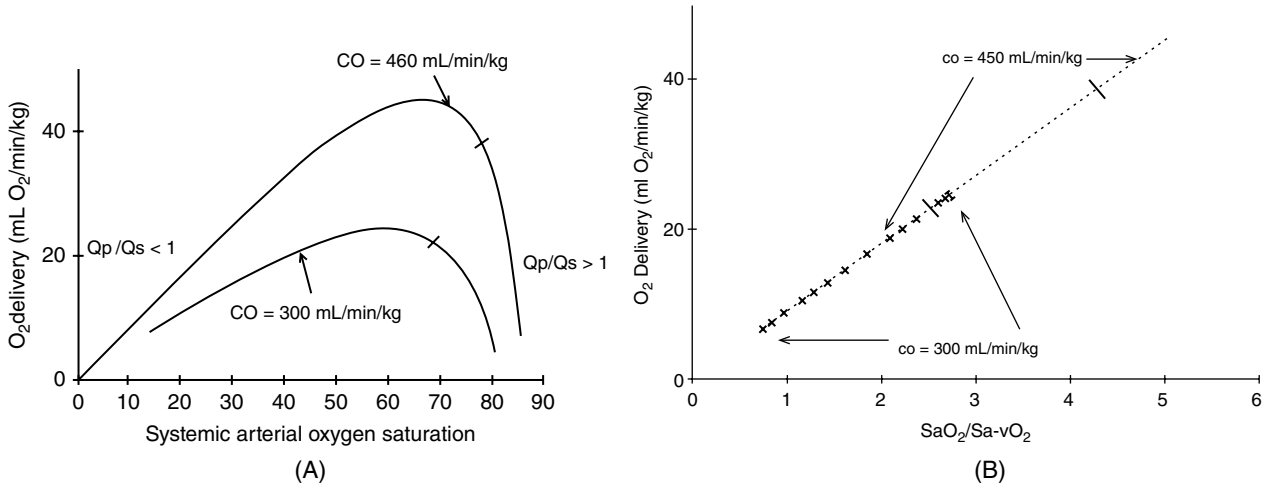


Figure 21.12 Simulations of the relationship between oxygen-derived parameters and systemic oxygen delivery (DO_2) following the Norwood operation. The curves shown in panel A were generated by setting the cardiac output (CO) at 300 and 450 mL/min/kg and varying the Q_P/Q_S ratio from 0.2 to 10. The short line on each curve represents the point at which $Q_P/Q_S = 1$. Note that similar low and high DO_2 can be generated with several combinations of CO and SaO_2. As an example, at a SaO_2 of 70%, DO_2 can range between 21.9 and 45 mL O_2/min/kg, depending on CO. Note that in the region of the curves, where $Q_P/Q_S > 1$, small variations in SaO_2 result in large changes in DO_2. As an example, for the curve generated by setting CO at 450 mL/min/kg, increasing SaO_2 from 80 to 85%, decreases DO_2 from 34.1 to 14.6 mL/min/kg. By contrast, as shown in panel B, the oxygen excess factor ($\Omega = SaO_2/(SaO_2\text{-}SvO_2)$) is independent from the CO, whether 300 mL/min/kg (light dashed line with Xs) or 450 mL/min/kg (heavy dashed line), and it has a linear relationship with the systemic DO_2. (Source: From Barnea et al. [9]. Reproduced with permission of Wolters Kluwer Health, Inc.)

degrees of capillary leak syndrome, and concomitant organ dysfunction.

In the postoperative setting of CHD surgery, ultrasonography has become a standard diagnostic and monitoring tool. Although there are no specific recommendations in the CHD surgery setting, the international Euro-American panel of pediatric and neonatal experts in Point-of-care ultrasound of the ESPNIC has recently reviewed the literature and established guidelines for the ultrasound-based monitoring of critically ill children [150]. Ultrasonography is an excellent tool to obtain hemodynamic information and aid clinical decision making by assessment of preload, of fluid responsiveness, of pulmonary artery pressure along with diagnosis of pericardial effusion and qualitative assessment of cardiac function. Lung ultrasonography may also be helpful to detect pneumonia, pneumothorax, or pleural effusions, and particularly to evaluate lung edema in the context of heart failure [151].

Assessment of cardiac output

In current practice, direct measurement of cardiac output is rare. However, our ability to accurately estimate CO, based on clinical parameters, is poor [131]. The clinical estimate of CO is even more challenging in single-ventricle patients with parallel circulation. The assumption that objective measurement, and hence manipulation, of hemodynamic variables may improve outcome, supports the need for a safe, accurate and repeatable technique for measurement of cardiac index in critically ill children. Unfortunately, the use of invasive techniques, such as percutaneous insertion of pulmonary artery catheters, may be judged to have an unfavorable risk/benefit ratio in children, despite their ability to provide information relevant to optimizing CO. The main technologies and devices used to monitor CO following CHD surgery in children are listed in Table 21.7. They are all based by on the estimation of the stroke volume. Thus, the sinus rhythm is required to derive an accurate CO estimate.

Systems for monitoring cardiac output

Intermittent thermodilution through a pulmonary artery catheter has been the gold standard method for CO monitoring since the late 1960s. This method is, nevertheless, invasive, so that, the use of the pulmonary artery catheter decreased in the 1990s. Development of the less invasive monitoring of CO using the transesophageal Doppler started in the 1990s. The ESPNIC recommendations for the monitoring of critically ill children [147] propose ultrasound-based methods for the initial assessment of unstable patients. Thermodilution techniques are reserved for cases in which reliable absolute CO measurements are deemed necessary, and for which it is recommended to use an invasive and, if possible, continuous CO monitoring [147].

Transpulmonary dilution methods. Transpulmonary thermodilution (TPTD) was developed in the 1990s. Although less invasive than the initial thermodilution method through a pulmonary artery catheter, a dedicated central venous line and a central arterial line are required. In contrast to the pulmonary artery catheter method, cold saline is injected in a central vein instead of the RA, and blood temperature is measured in a systemic artery instead of the pulmonary artery. TPTD estimates CO through the analysis of the arterial thermodilution curve, and, according to the Stewart–Hamilton equation, CO is inversely proportional to the area under the indicator time curve. TPTD has the unique advantage of being able to estimate at the bedside extravascular lung water, which quantifies the volume of pulmonary edema and quantifies the degree of a pulmonary capillary

Table 21.7 Nonexhaustive list of the available cardiac output monitoring systems validated in children with congenital cardiac operations

Technology	System	Invasiveness	Mechanism	Advantages	Clinical issues
Transpulmonary dilution methods	Vigilance II® (Edwards Lifescience, Irvine, CA, USA)	++	TPTD	Gold standard for continuous CO monitoring. Continuous pulmonary pressure and SvO_2 monitoring	Requires a dedicated central venous catheter and a femoral artery catheter.
	COstatus® (Transonic Systems Inc, Ithaca, NY, USA)	++	Transpulmonary ultrasound dilution with saline	Uses an existing central venous and arterial catheter Quantification of intracardiac shunts.	Intermittent CO estimation. Sensitive to changes in vasomotor tone
Ultrasound-based methods	CardioQP® (Deltex Medical; Irving, Texas, USA)	0/+	Transesophageal Doppler ultrasound	Continuous CO monitoring Minimally invasive	Requires manipulation for proper position Operator-dependent
	USCOM® (USCOM Ltd, Sydney, New South Wales, Australia)	0	Suprasternal Doppler ultrasound	Noninvasive CO measurement	Intermittent CO estimation Operator-dependent
Pulse contour analysis	PICCO® (Pulsion, Feldkirchen, Germany)	++	Pulse contour analysis Calibration by TPTD	Continuous CO monitoring. Continuous SvO_2 monitoring. Good accuracy.	Requires a central venous catheter and a specific femoral artery catheter. Requires periodic external calibration by TPTD.
	FloTrac/Vigileo® (Edwards Lifescience, Irvine, CA, USA)	+	Pulse contour analysis	Continuous CO monitoring. Self-calibration.	Requires a dedicated arterial catheter. Sensitive to changes in vasomotor tone.
	Mobil-O-Graph® (I.E.M GmbH, Stalberg, Germany)	0	Pulse contour analysis through a cuff placed around the arm.	Continuous CO monitoring. Self-calibration.	Only investigated in patients > 10 years
	ClearSite® (Edwards Lifescience, Irvine, CA, USA) Formerly known as Nexfin®	0	Pulse contour analysis through a finger cuff with infrared photoplethysmography	Continuous CO monitoring. Self-calibration.	Motion artefacts
Thoracic bioimpedance	ICON® (Cardiotronic/Osypka Medical, Inc, La Jolla, CA, USA)	0	Bioimpedance In small infants: 4 electrodes placed on the left leg, chest, neck and cheek or forehead In older children: 4 electrodes placed on the left chest and left side of the neck	Continuous CO monitoring	Reliable in critically ill patients 1 day to 19 years old
	Aesculon® (Osypka, Medical GmbH, Berlin, Germany and San Diego, CA, USA)	0	Bioimpedance 4 electrodes placed on the left chest and left side of the neck	Continuous CO monitoring	Underestimates CO in children
	PhysioFlow® (Neumedx, Philadelphia, PA, USA)	0	Bioimpedance 6 electrodes placed on the thorax and left side of the neck	Continuous CO monitoring	Underestimates CO in children
Bioreactance	NICOM® (Cheetah Medical, Wilmington, Delaware, USA)	0	Bioreactance 4 double electrodes placed on the thorax.	Continuous CO monitoring	Reliable CO values in patients > 10 kg with normal heart anatomy CO values not reliable in patients with cardiac defects

CO: Cardiac output; TPTD: Transpulmonary thermodilution; ++: Invasive; +: Minimally invasive; 0: Noninvasive
(Source: Adapted from Ramsingh et al. [152] and van Wijk et al. [153].)

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leak. The new Vigilance II monitor (Edwards Lifescience, Irvine, CA) uses thermal energy emitted by a filament located on the catheter to continuously calculate cardiac output using the thermodilution principle. TPTD is implemented and serves for the external calibration of several pulse contour analysis monitors.

COstatus (Transonic Systems Inc., Ithaca, NY, USA) is a novel monitoring device, which uses an extra-corporeal arterio-venous loop and two ultrasound sensors, one on each side of the loop. The changes in the transit time of the ultrasound beam, crossing the loop when body temperature saline is injected, are used to calculate CO via the Stewart–Hamilton equation. COstatus is considered an accurate CO monitor in infants [154].

To obtain a reliable measurement of CO using transpulmonary dilution methods, the following conditions must be met: (i) constant blood flow; (ii) minimal loss of the indicator; (iii) complete mixing of the indicator in the blood; and (iv) a single passage of the indicator. Several of these conditions are violated after CHD surgery. The blood flow is not constant in the presence of valvular regurgitations. Left-to-right intra- or extracardiac shunting (collaterals) result in loss of the indicator. Finally, there is always a degree of recirculation of the indicator, which increases in the presence of a right-to left intracardiac shunting. In such situation, continuous CO monitoring is still feasible, although it should be viewed as a method that measures a trend rather than an absolute value. In a very original manner, using data from the aforementioned artifacts, the COstatus monitor can detect shunts and estimate the Q_P/Q_S ratio of the intracardiac shunts [155].

Ultrasound-based methods quantify the stroke volume (and hence the CO) by measuring the aortic or pulmonary valve velocity time integral, and the valve annulus diameter. The technique requires a trained operator and can be performed using transthoracic and transesophageal echocardiography. Transesophageal Doppler probes have been designed specifically to assess descending aortic flow and to calculate CO, with either a built-in nomogram or M-mode measurement to calculate the aortic diameter. Decreasing probe sizes allow placement in pediatric patients of ≥3 kg. Major biases, however, may prevent the correct estimation of CO using transesophageal Doppler [156]. Errors are due to the angle of insonation, the assumption of specific flow profiles across the vessels when calculating average flows, and to the measurement of the cross-sectional area of the vessel being imaged. Additionally, the assumption is made that there is a constant flow between the ascending and the descending aorta, which is not always the case in the setting of CHD. Finally, the measurement is highly operator-dependent because the device requires manual positioning of the probe for optimum signal acquisition. The reported accuracy of ultrasound-based methods is controversial; when compared with TPTD, minimally invasive techniques like the CardioQP esophageal Doppler monitor underestimates CO [157, 158], whereas the ultrasonic cardiac output monitor (USCOM) appears reliable in children when operated by trained users [159]. Normal ranges of the cardiovascular parameters measured using the USCOM have recently been published for a large age range [160].

Pulse contour analysis of intra-arterial blood pressure waveform is used by mini-invasive systems aiming to estimate CO continuously. The arterial pressure waveform is a complex physiological signal that is determined by the interaction of LV stroke volume, SVR, and vascular compliance. Thus, the CO estimate is highly dependent on vasomotor tone and vascular compliance, and, because of the nonlinear pressure–volume relationship within the arterial circulation, requires repeated recalibration by a compliance independent system. The pulse contour analysis monitors are more or less invasive, depending on the arterial pressure measurement method: dedicated arterial catheter or external sensor/finger cuff, and on the calibration method: external calibration by TPTD or self-calibration. Minimally invasive devices require an arterial catheter, whereas noninvasive devices use the volume clamp method by a finger cuff, or applanation tonometry by a sensor placed on the skin over the radial artery. External calibration uses TPTD, whereas self-calibration is based on the compensation for aortic compliance using demographic and biometric data, and on the estimation of the vascular tone from the mean arterial pressure. Relatively little and somewhat disappointing data are available in the setting of CHD surgery. The PICCO® (Pulsion, München, Germany) device has been validated in CHD surgery, and found to be as accurate as TPTD [161]. Frequent recalibration is required when the vasomotor tone changes, which is the case in the postoperative cardiac setting. The Mobil-O-Graph® (I.E.M GmbH, Stolberg, Germany) device has been used in patients older than 10 years; at low CO values, however, the monitor overestimated the CO when compared with echocardiography measurements [162]. In children with cardiac transplant, cardiomyopathies or PHT undergoing cardiac catheterization, the FloTrac®-estimated CO showed poor agreement with TPTD [163].

Bioimpedance cardiometry measures changes in thoracic electrical bioimpedance during the cardiac cycle via electrodes placed on the skin. The change in orientation of the red blood cells in the aorta, from random during diastole to an aligned or parallel orientation during systole, causes changes in electrical conductivity and electrical impedance. Electrovelocimetry relates the maximum rate of change of impedance to peak aortic blood acceleration during the cardiac cycle to estimate stroke volume. Reported accuracy of these devices on pediatric populations is controversial. In an observational study, the ICON® device provided real-time hemodynamic information regarding developing hemodynamic events and successfully tracked the rapid response to interventions in children 1 day–19 years old [164]. The Aesculon® monitor (Osypka Medical, Berlin, Germany and San Diego, CA, USA) is one of the most studied in CHD surgery setting. It provides CO estimates which showed good agreement with those derived from the direct Fick-oxygen principle in children undergoing diagnostic heart catheterization [165]. In neonates undergoing the arterial switch operation, it provides similar estimates to those derived by transthoracic Doppler-estimated CO [166]. However, the same device underestimated the CO when compared with transthoracic echocardiography in older infants [157], and underestimates the CO when compared with TPTD [167]. Similar results were reported with the PhysioFlow® device

(NeuMeDx, Philadelphia, PA) during cardiac catheterization in children with CHD [168]. Arrhythmia and pleural effusions may limit its use.

Bioreactance cardiometry is the analysis of the variation in the frequency spectra of a delivered oscillating current that occurs when the current traverses the thoracic cavity. The NICOM® monitor (Cheetah Medical, Wilmington, Delaware, USA) provided CO values which showed a good correlation with echocardiography-estimated CO in pediatric patients > 10 kg with normal heart anatomy, but underestimated CO in patients with ventricular septal defects [169].

Despite lots of efforts to implement them, the reliability of such mini- or noninvasive devices is under question. A meta-analysis of CO monitoring devices in adults found that no noninvasive device or technology was interchangeable with TPTD: the percentage of error was 42% for bioimpedance and 45% for noninvasive pulse contour analysis, where a maximum of 30% error is considered acceptable [170]. A meta-analysis of mini-invasive CO monitors in children showed that bioimpedance cardiometry provided the smallest bias and lowest percentage error when compared with TPTD [171].

Near infra-red spectroscopy

Near-infrared spectroscopy (NIRS) provides real time information regarding regional tissue oxygenation (rSO2) and oxygen uptake/consumption balance in a volume of tissue to a depth of approximately 2.5–3 cm. The parameter displayed is a relative number calculated using an algorithm calibrated from *in vivo* and *in vitro* models. In children with CHD requiring CPB, prolonged perioperative cerebral desaturation < 45%, as assessed by NIRS, has been associated with reduced DO_2 and/or increased extraction rate of the brain, abnormal brain magnetic resonance findings, and worsened neurodevelopmental outcomes [172, 173]. Phelps et al. reported that a cerebral rSO_2 value below 55% in the first 48 hours after surgery had been highly predictive of an adverse outcome in 50 infants who had undergone the Norwood procedure [174]. Therefore, cerebral NIRS monitoring has become a standard in many pediatric cardiac centers.

Despite significant efforts during the last two decades aiming at the definition of normal ranges and lower safety margins, consensus regarding these important targets has not yet been reached. Pediatric anesthesiologists have adopted common adult patient intervention limits like an absolute value <55% or a 20% drop from baseline. These thresholds have been recently questioned, since it has been shown that a decrease in perioperative cerebral rSO_2 of less than 20% is associated with negative behavioral changes on postoperative day 7 in noncardiac pediatric patients [175].

However, an NIRS monitoring strategy focusing exclusively on the brain is inappropriate to assess the amount of O_2 available to organs with perfusion regulated by different neurohormonal mechanisms, and the concept extended from the initial purpose of cerebral monitoring. Multisite NIRS monitoring is a new trend, with some initial evidence of its capability to detect early stage LCOS. Several authors showed that the linear combination of postoperative somatic and cerebral rSO_2 is a reliable indicator of postoperative LCOS, lactate concentration, morbidity and mortality [176, 177]. Averaged cerebral and renal rSO_2 < 65% predicted a lactate level > 3 mmol/L within 24 hours of CHD surgery [176].

Hoffman et al. [177] designed an original two-site method using cerebral and somatic probes. Oxygen extraction by the brain is high (about 35%), and flow–metabolism coupling is achieved by an autoregulatory mechanism. By contrast, the oxygen extraction of the kidney is low (10–15%), and renovascular resistance is under tight sympathetic control. Under normal conditions, renal rSO_2 is 15–20% higher than brain rSO_2. In the early stage of LCOS, the vascular resistance increases, and flow is redistributed to preserve cerebral blood flow at the expense of somatic perfusion: the perfusion of the kidney and renal rSO_2 are expected to drop dramatically, whereas cerebral rSO_2 remains high, and the gradient narrows or becomes negative. According to Hoffman et al. [177], the somatic–cerebral rSO_2 gradient below 10%, can be used to assess shock and the risk of anaerobic metabolism, as suggested in Figure 21.13. In infants at rest, somatic sensors provide similar rSO_2,

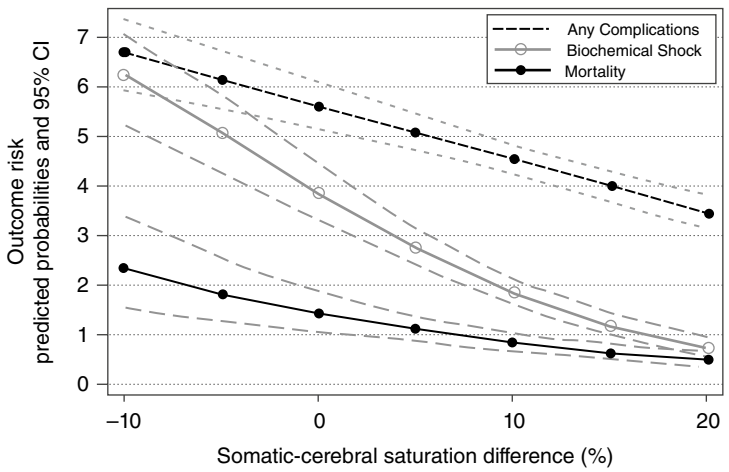


Figure 21.13 The somatic–cerebral saturation gradient estimates the adequacy of DO_2 and is associated with outcome. Data from the Children's Hospital of Wisconsin hypoplastic left heart syndrome stage I perioperative database comparing the probability of complications and postoperative somatic–cerebral saturation gradient assessed hourly for 48 hours. (Source: From Tweddel et al. [177]. Reproduced with permission of Elsevier.)

regardless of whether they are positioned on the kidney, arm, or thigh; however, renal rSO_2 has the largest variability in response to flow and pressure variations [178], suggesting that monitoring of renal rSO_2 may provide the largest amount of information with regard to somatic perfusion.

NIRS measures of hemoglobin saturation are heavily venous-weighted, correlate with regional venous saturation, and can, therefore, be used as a noninvasive surrogate for regional SvO_2. This enables the calculation of another increasingly used parameter, fractional regional tissue oxygen extraction:

$$\text{FTOE} = \frac{(SaO_2 - rSO_2)}{SaO_2} \tag{21.19}$$

This composite parameter reflects the regional DO_2/consumption balance, and represents an estimation of end-organ perfusion. Because different organs have different flow–metabolism relationships, estimation of global oxygen economy is improved by probing fractional tissue oxygen extraction (FTOE) from multiple organ beds. NIRS is currently the best available tool to continuously and noninvasively measure regional tissue-oxygenation and perfusion.

Several factors may interfere with the NIRS measurements. Those that are specific to its use as a cerebral monitor include $PaCO_2$, cerebral autoregulation, and extracerebral contamination of the signal, while others include light contamination, interference between the two probes, dark skin, the arterio-venous ratio in the tissue, and drugs that modify vasomotricity. The use of the somatic–cerebral rSO_2 gradient avoids the variability of the NIRS signal related to cyanosis.

Mixed venous saturation

Mixed venous saturation (SvO_2) provides an estimate of global oxygen balance by measuring the postextraction systemic O_2 saturation, and it is therefore more directly related to tissue oxygenation than to CO measurement.

If we ignore dissolved oxygen, then equation (21.1) can be rewritten as

$$\text{OER} = \frac{(SaO_2 - SvO_2)}{SaO_2} \tag{21.20}$$

Thus

$$SvO_2 = (1 - \text{OER}) \times SaO_2 \tag{21.21}$$

and since SaO_2 is often kept > 0.9, one can roughly estimate that

$$SvO_2 = 1 - \text{OER} \tag{21.22}$$

This simple relationship indicates that SvO_2 is directly related to OER [179]. The critical OER level defined by the onset of anaerobic metabolism is approximately 0.5–0.6. Therefore, it follows that the critical SvO_2 is approximately 40–50%. SvO_2 levels less than 50% should be carefully considered and acted upon and SvO_2 levels between 50 and 70%, therefore, low, must be interpreted in the context of the adequacy of tissue oxygenation [18].

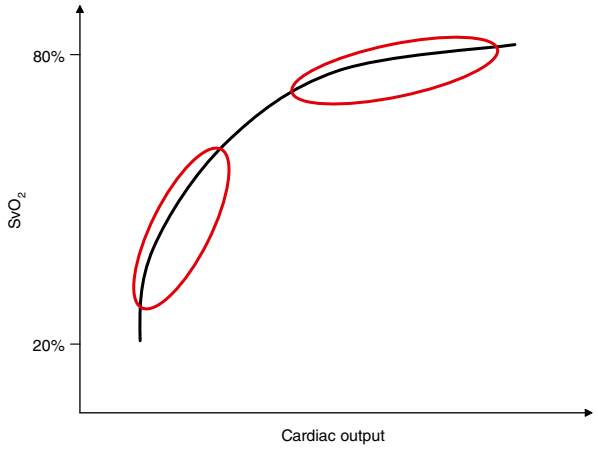


Figure 21.14 The relationship between mixed venous saturation (SvO_2) and cardiac output, based on the Fick equation. (Source: Adapted from Walley [179].)

The O_2 extraction and, thus, venous saturation levels vary across various organs and SvO_2 is a mix of venous saturation of all organs. As CO falls, blood flow is redistributed to maintain vital organ perfusion. Oxygen saturation falls first in the IVC, and it is accompanied by a less severe drop in SvO_2. As CO falls further, the SVC and jugular saturations begin to decrease. Figure 21.14 illustrates the relationship between CO and SvO_2 according to the Fick equation, and suggests that when CO is high, minor variations in CO are related to large variations in SvO_2, and that when CO is low, large variations in CO are related to minor variations in SvO_2. Thus, SvO_2 measurements perform poorly when SvO_2 is clinically irrelevant (high CO) but perform well in clinically relevant situations where DO_2 may be inadequate.

A true SvO_2 should reflect complete mixing of the returning systemic venous blood, making the pulmonary artery the most accurate sampling site. The difference between the venous saturation when drawn from a thoracic central line with the tip placed in the RA or SVC ($ScvO_2$) and SvO_2 is primarily due to mixing of less saturated blood from the coronary sinus in the RA. However, the heterogeneity of flow and metabolic demand within and between organs under critical conditions, and decreased cerebral oxygen uptake during sedation, also play a role. Nevertheless, there is an excellent correlation between SvO_2 and the $ScvO_2$.

$ScvO_2$ has the potential to predict adverse events following CHD surgery [180]. A $ScvO_2$ drop to 40% for more than 18 min, or below 50% for more than 35 min, were highly predictive of multiorgan failure, reoperation or reopening of the chest, and a need for extracorporeal support [180]. Following the Norwood operation, reductions in SvO_2 reflected tissue hypoxia despite apparently normal hemodynamic parameters, and continuous SvO_2 monitoring has the potential to improve survival [181]. Data from continuous $ScvO_2$ monitoring demonstrated that only 32% of the SvO_2 variance could be explained by SaO_2 variations following the Norwood operation, and that the main driver of DO_2 improvement was intense afterload reduction [81].

The interpretation of SvO_2 following early palliation with systemic-to-pulmonary anastomosis in infants with a functionally univentricular hearts require some special attention.

Traditionally, SaO_2 has been used as a rough index of Q_P/Q_S ratio, and systemic vasoconstriction has been reported in response to failing systemic perfusion at SaO_2 above 80%. It has also been suggested that SvO_2 levels as low as 55% may represent ideal hemodynamics for a patient with a single ventricle [182] due to complete mixing of the arterial and venous blood. Using computer simulations to study the single-ventricular circulation, Barnea et al. [9] provided a subtle interpretation of the oxygenation parameters. The total CO is distributed from a single ventricular stroke volume to the systemic and pulmonary circulations. The relative distribution of flow is dictated by their respective vascular resistances. Slight increases in SaO_2 may be associated with large decreases in DO_2, as shown in Figure 21.12, panel A. Also, high values of the Q_P/Q_S ratio are always associated with low DO2, which is only partially compensated by increases in CO. Ideally, the Q_P/Q_S ratio should be kept below 1.5, therefore, a Q_P/Q_S ratio between 0.8 and 1.2 and $SvO_2 > 50\%$ have been provided as targets for hemodynamic optimization [81]. However, taken alone, SaO_2, SvO_2, or the Q_P/Q_S ratio cannot be used to maximize DO_2, and equation (21.9) shows that DO_2 is a complex function of both the CO and the Q_P/Q_S ratio. The index that should best guide therapy to increase DO_2 is the oxygen excess factor:

$$\Omega = DO_2/VO_2 \tag{21.23}$$

If dissolved oxygen is ignored, then this can be rewritten as

$$\Omega = \frac{SaO_2}{(SaO_2 - SvO_2)} \tag{21.24}$$

A linear relationship has been demonstrated between Ω and DO_2, irrespective of the CO, as shown in Figure 21.12, panel B [9]. The normal ratio is of 4 to 5 times the amount of DO_2 to VO_2. It is commonly accepted that Ω should be beyond 3.5 following the Norwood procedure, and any intervention that increases Ω is considered beneficial (Box 21.4).

The interpretation of SvO_2 following CHD surgery can be overestimated in the presence of residual left-to-right shunting. Also, because sympathetic tone increases vascular resistance in splanchnic-mesenteric beds as CO falls, the relative contribution of desaturated blood from those regions to the measured SvO_2 level is reduced and critical regional ischemia may occur in the absence of a critical reduction in whole-body SvO_2.

Box 21.4: Oxygen extraction ratio and mixed venous oximetry

Oxygen extraction ratios based on mixed venous oximetry
- 25% – normal
- 30–40% – increased
- 40–50% – impeding shock
- 50–60% – shock, elevated lactate levels

Normal oxygen extraction ratios for central venous oximetry
- Right atrium – 25%
- Jugular vein – 35%
- Superior vena cava – 30%
- Inferior vena cava – 20%

Source: Adapted from Bronicki et al. [18].

Blood lactate

The majority of the ATP pool is produced via oxidative phosphorylation, which generates 36 molecules of ATP/molecule of glucose. The first stage of oxidative phosphorylation is the conversion of glucose to pyruvic acid, which occurs in the cytoplasm. The second stage is the oxidation of pyruvic acid into acetyl coenzyme A, which occurs in the mitochondria as part of the Krebs cycle. Lactate is generated by the reaction between pyruvic acid and reduced nicotinamide adenine dinucleotide (NAD) and requires either oxygen for reconversion into pyruvic acid or energy for conversion to glucose. The normal lactate/pyruvate ratio is approximately 10:1.

Oxidative phosphorylation can only occur when the mitochondrial PO_2 is > 1 mmHg (normally in the order of 4–20 mmHg). Connett et al. [183] defined the thresholds of cell hypoxia 40 years ago. The first threshold is crossed when cell oxygen decreases, but ATP production is maintained at a level sufficient to match ATP demand by metabolic adaptation: increase in glycolysis and changes in the phosphorylation state of the mitochondria. The second threshold is crossed when the steady state of ATP turnover can only be maintained by supplementary production of ATP via anaerobic glycolysis. This is a low efficiency pathway which results in only two molecules of ATP per molecule of glucose and leads to rapid ATP depletion in high energy-consuming organs, such as the brain, liver, and kidney. At this stage, ATP production becomes oxygen limited, a state that defines dysoxia.

During hypoxia, the consumption of glucose increases to 90% of the total substrate consumed. It follows, therefore, that excess lactate accumulates under anaerobic conditions. The normal reference value for lactate in critically ill patients is traditionally considered to be <2 mmol/L. Lactic acidosis develops when the lactate concentration exceeds 5 mmol/L. The rapid increase in lactate production following exposure to hypoxia has been demonstrated experimentally: when PaO_2 decreased from 100 to 40 mmHg, lactate levels increased from 2 to 6 mmol/L within 15 min, reaching 10 mmol/L within 30 min [184]. Likewise, restoration of normal DO_2 results in a rather prompt return to normal levels [185]; the half-life of lactate in the blood is less than 10 min.

For many years, blood lactate levels have been seen as a surrogate marker of CO and used to predict outcomes in high-risk patients [186, 187]. Charpie et al. found that increased initial lactate levels or an increase in lactate of 0.75 mmol/L per hour after complex CHD surgeries were associated with a poor outcome [186]. Rossi et al. incorporated serial lactate measurements into a therapeutic algorithm during the postoperative period aiming to increase the DO_2 and/or decrease the VO_2; blood lactate levels that continued to increase or remained persistently high (>10 mmol/L) despite maximal medical therapy were taken to indicate a requirement for mechanical cardiopulmonary support, as shown in Figure 21.15 [187]. The result was a three-fold reduction in mortality in high-risk patients [187]. Unlike SvO_2, lactate levels have the same significance in single-ventricle patients as they do in patients with biventricular physiology. A persistent lactate concentration >10 mmol/L always indicates severe physiologic derangement and increased risk for mortality.

There are several biases in the interpretation of mild hyperlactatemia. The use of epinephrine creates a disparity

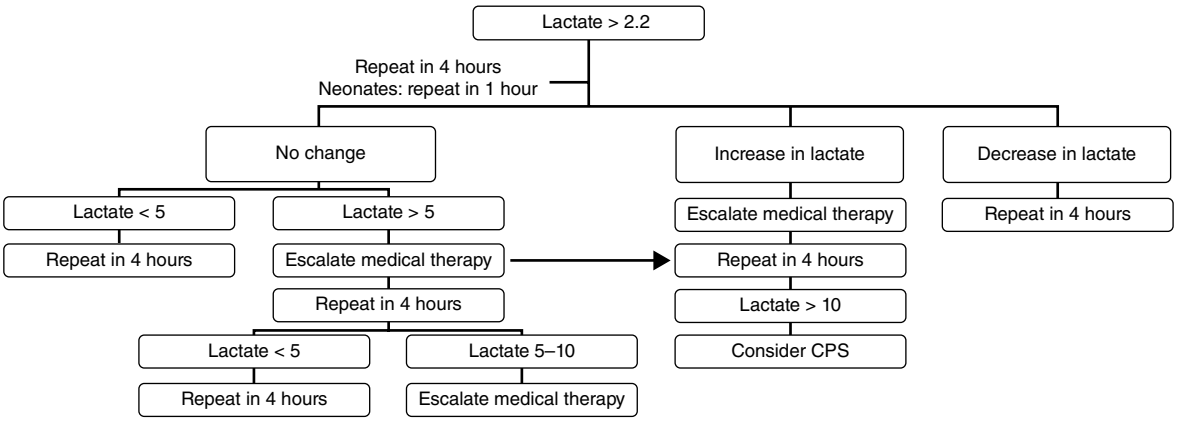


Figure 21.15 Example of algorithm for the postoperative management of patients based on serial lactate determinations. (Source: Rossi et al. [187]. Reproduced with permission of Springer Nature.)

between the rate of peripheral glycolysis and mitochondrial oxidative capacity through increased muscular and hepatic glycogenolysis (via a β_2-adrenergic stimulation), through inhibition of glycogen synthesis, and through limitation of the rate at which pyruvic acid enters the Krebs cycle. As it accumulates, pyruvic acid is converted into lactate so as to preserve intracellular supplies of NAD and ATP. Lactate also accumulates if hepatic and renal clearance is impaired. Lactate delivery via red blood cell transfusions may also result in mild hyperlactatemia [188].

Central venous to arterial CO_2 difference

Venous to arterial CO_2 partial pressure difference ($AVCO_2$) measures the circulatory clearance of tissue CO_2 and is correlated with CO. Under aerobic conditions, CO_2 is the end product of all energy production pathways. Under anaerobic conditions, there is an extra CO_2 production which results from the buffering of lactic acidosis by bicarbonate. CO_2 is extremely diffusible and its elimination through the lungs is not impaired during LCOS, therefore, $PaCO_2$ will remain normal even in the case of profound acidosis, whereas the venous CO_2 will increase. Widening of $AVCO_2$ represents an imbalance between CO and tissue CO_2 production. The potential to detect acidosis through capnography is well known, however, exhaled CO_2 is multifactorial and difficult to monitor in patients on spontaneous ventilation. Importantly, the correlation between $AVCO_2$ and CO is not influenced by pulmonary venous desaturation, intracardiac shunting and anemia, which may decrease DO_2 independent of CO, and which impact oxygen-derived parameters, such as $ScVO_2$. For the same reason, $AVCO_2$ measurements are valid in patients with single ventricle, and have a stronger correlation with CO compared with oxygen-derived parameters. An observational study in patients < 90-day old undergoing cardiac surgery reported an independent association between $AVCO_2$ at admission to the cardiac PICU and postoperative mortality [189]. Patients with poor outcome had a median $AVCO_2$ of 8.3 mmHg upon admission, whereas those with a good outcome had a median 5.4 mmHg. Importantly, $AVCO_2$ increased over the hours following PICU admission and peaked after 12–24 hours at a median of 10.5 mmHg: this evolution over time may mirror the presence of postoperative LCOS.

Current practices

Monitoring practices vary worldwide. Among the respondents at the 2014 PCICS survey [26] 99% reported monitoring lactate and 89% reported monitoring SvO_2; only 25% of the respondents, however, reported using multisite NIRS and only 32% exploited the core peripheral temperature gap. Among pediatric cardiac anesthesiologists in the United States, a larger percentage (78%) are reported to routinely use multisite NIRS monitoring in combination with serial lactate measurements [190]. The PCICS respondents used echocardiography routinely as a tool for hemodynamic monitoring in 53% of cases and used minimally invasive CO monitoring or Doppler hemodynamic CO monitoring in 3% of cases. An Italian survey among pediatric cardiac centers revealed the availability of pulmonary arterial catheter and TPTD in 43% of the centers, and pulse contour methods in 29% of the centers [191], although the percentage of cases in which these tools were indeed used to monitor patients was not reported.

It appears, nevertheless, that the estimation of the VO_2/DO_2 balance relies more on surrogate markers than on more accurate and invasive measurement methods. This is coherent, knowing that even accurate CO measurements might be misleading during the postoperative period: a normal CO might be inadequate at times of increased oxygen demand, and a lower CO may be sufficient during times of lower oxygen demand. Besides, intracardiac shunting and small patient size make techniques, such as thermodilution CO monitoring difficult. Surrogate markers, such as SvO_2 and lactate concentration are predictors of adverse clinical outcomes. Nevertheless, the inability to readily and reliably assess global and regional tissue perfusion remains a challenge in this patient group. Therefore, the use of NIRS measured regional saturations might become a central parameter.

KEY POINTS: MONITORING

- Invasive and noninvasive CO monitors have limited utility in CHD surgery and to date have not been demonstrated to improve outcome.
- NIRS is the best monitor to date for tissue oxygenation, can predict low CO and poor outcome.

- Mixed venous saturation and blood lactate concentration are excellent and very popular surrogate estimators of the VO_2/DO_2 balance, their serial measurements can predict poor outcome.

Conclusion

The fundamental requirement of postoperative hemodynamic management is to match oxygen consumption and delivery, in order to prevent oxygen debt and sustain cellular metabolism. Although the quest for new therapeutic possibilities is ongoing, it is likely that one of the greatest opportunities comes from using existing therapies more effectively. The indicators used to achieve the desired therapeutic goal must be easy to obtain and safe, and invasive techniques may be judged to have an unfavorable risk/benefit ratio in children. Nevertheless, it is unwise to focus on maximizing DO_2 and/or minimizing consumption alone, while ignoring regional and tissue perfusion. Therefore, hemodynamic monitoring requires a paradigm shift towards tissue oxygenation, away from more conventional parameters. Finally, our therapeutic interventions must be associated with an improved outcome; as such, the impact on surrogate physiological endpoint is insufficient evidence of clinical efficacy.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995:92(8):2226–2235. The classic paper using thermodilution cardiac output measurements in infants, describing the predictable postoperative decline in cardiac output in the first 24 hours after surgery.

4 Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107(7):996–1002. The first report of the randomized, blinded trial of milrinone in pediatric cardiac surgery reporting that high-dose milrinone prevents LCOS.

5 Li J, Zhang G, McCrindle BW, et al. Profiles of hemodynamics and oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure. J Thorac Cardiovasc Surg 2007;133(2):441–8. A study of hemodynamic and oxygen transport balance after the Norwood operation, providing important insights into desirable goals for management in the realy postoperative period.

33 Oualha M, Urien S, Spreux-Varoquaux O, et al. Pharmacokinetics, hemodynamic and metabolic effects of epinephrine to prevent post-operative low cardiac output syndrome in children. Crit Care 2014;18(1):R23. An important study of epinephrine pharmacokinetics, pharmacodynamics, and metabolic effects in children, including a new dosing model.

81 Hoffman GM, Tweddell JS, Ghanayem NS, et al. Alteration of the critical arteriovenous oxygen saturation relationship by sustained afterload reduction after the Norwood procedure. J Thorac Cardiovasc Surg 2004;127(3):738–45. An important hemodynamic study after the Norwood stage I palliation demonstrating the benefits of afterload reduction to improve DO_2.

92 Miller OI, Tang SF, Keech A, et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet 2000;356(9240):1464–9. A landmark trial for the preventive use of inhaled nitric oxide following cardiac surgery in patients at righ risk of pulmonary hypertension.

122 Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. J Clin Invest 1966;45(3):399–411. The classical paper demonstrating that increasing pH, whether by increasing minute ventilation or decreasing hydrogen ion concentration, will lower pulmonary vascular resistance.

132 Shekerdemian L. Perioperative manipulation of the circulation in children with congenital heart disease. Heart 2009;95(15):1286–96. An excellent review of the hemodynamic management and of cardiopulmonary interactions, highlighting the need for an individualized strategy, based on the pathophysiology of each type of CHD.

138 Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. Arch Dis Child 1999;80(5):475–80. An excellent review article presenting the effects of positive perssure ventilation on the cardiovascular system.

173 Kussman BD, Wypij D, Laussen PC, et al. Relationship of intraoperative cerebral oxygen saturation to neurodevelopmental outcome and brain magnetic resonance imaging at 1 year of age in infants undergoing biventricular repair. Circulation 2010;122(3):245–54. An important study demonstrating the neurodevelopmental impact of intraoperative cerebral desaturation.

174 Phelps HM, Mahle WT, Kim D, et al. Postoperative cerebral oxygenation in hypoplastic left heart syndrome after the Norwood procedure. Ann Thorac Surg 2009;87(5):1490–4. An important study demonstrating that cerebral oxygenation is a potential surrogate of global oxygen transport balance, and that low saturation is associated with cardiac arrest and ECMO cannulation.

180 Crowley R, Sanchez E, Ho JK, et al. Prolonged central venous desaturation measured by continuous oximetry is associated with adverse outcomes in pediatric cardiac surgery. Anesthesiology 2011;115(5):1033–43. An important study demonstrating the utility of continuous central venous oxygen saturation monitoring in high-risk pediatric CHD patients.

186 Charpie JR, Dekeon MK, Goldberg CS, et al. Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. J Thorac Cardiovasc Surg 2000;120(1):73–80. A study that laid the foundation for the current use of serial lactate measurement in neonatal cardiac surgery.

CHAPTER 22
Arrhythmias: Diagnosis and Management

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Introduction

The practice of pediatric cardiovascular anesthesiology has evolved significantly over the years, expanding beyond the operative setting to many non-surgical environments. Anesthetic care for infants, children, and adolescents who have or are at risk for, cardiac rhythm disturbances is now provided at various locations, including operating rooms, critical care units, emergency facilities, treatment rooms, and cardiac catheterization/electrophysiology laboratories. The same is true for other patients with congenital heart disease (CHD) beyond childhood. General knowledge of arrhythmia diagnosis and management is essential for anesthetic care in any of these settings, although in some cases, consultation with a specialist is required. This chapter provides a practical approach to pediatric cardiac arrhythmias and rhythm disturbances most commonly affecting patients with CHD, focusing on the diagnosis, mechanisms, and acute management strategies. A brief review of anti-arrhythmic drug (AAD) therapies and the basic principles of cardiac pacing in children, as applicable to the practice of anesthesia, is also presented.

Cardiac rhythm disturbances

Sinus bradycardia

Sinus bradycardia is characterized by a heart rate below the norm for the patient's age and by a normal, sinus P wave. Slow heart rates can be observed during sleep or may be secondary to a high vagal tone. During significant sinus bradycardia, an escape rhythm may arise from the atrium, junction, or ventricle. In otherwise healthy children, this is usually a benign rhythm with no hemodynamic consequences. Patients with certain forms of CHD, however, are more prone to slow heart rhythms that may indeed be clinically significant. Those with heterotaxy syndromes are included in this category because of the absence, displacement, or hypoplasia of the true sinus node in these patients [1].

Intraoperatively, sinus bradycardia can result from vagal stimulation during induction of anesthesia, laryngoscopy, endotracheal intubation, or tracheal suctioning. Sinus bradycardia may also be related to drug administration (e.g., opioids) or other mechanisms of increased parasympathetic activity. This type of sinus bradycardia rarely results in significant hemodynamic compromise and can usually be

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treated by removing the stimulus or by administering a chronotropic agent such as atropine or epinephrine (See Box 22.1). Slow sinus rates can be seen during cardiac surgical manipulations around the sinus node or after interventions such as the closure of atrial septal defects (ASDs) and cardiac transplantation.

Sinus bradycardia can also be due to hypoxemia, hypothermia, hypotension, drugs, acidosis, electrolyte abnormalities, or increased intracranial pressure. Hypoxemia-related bradycardia should be treated promptly with oxygenation and ventilation as appropriate. The approach to other forms of secondary sinus bradycardia should focus on addressing the underlying cause. For worrisome low heart rates, particularly in small infants, drugs such as atropine or glycopyrrolate, should be considered. Ongoing bradycardia with clinical evidence of compromised cardiac output requires immediate escalation of therapy that, in most cases, includes epinephrine administration, cardiopulmonary resuscitation, and consideration of temporary pacing.

Low atrial rhythm

A low atrial rhythm is characterized by atrial activation that spreads upward from a focus on the low atrium. The electrocardiogram (ECG) shows inverted P waves in the inferior leads (II, III, and aVF). A slow atrial rhythm implies that another region of the heart has assumed the pacemaker activity of the sinus node. Although this rhythm may be associated with conditions that affect sinus node function intraoperatively, it is most commonly the result of surgical manipulation (Figure 22.1). In most individuals, this is a normal variant and rarely has a hemodynamic consequence.

Box 22.1: Acute therapy of bradycardia

- Treat primary causes – hypoxemia, hypothermia, acidosis, hypotension, anemia, hypoglycemia, hypothyroidism
- Consider causative drugs – opioids, beta-blockers, digoxin
- Consider potential effect from cardiac surgical manipulation
- Drug therapy
  - Atropine – 0.02–0.04 mg/kg IV (minimum dose 0.1 mg; maximum dose 0.5 mg [child], 1.0 mg [adolescent])
  - Epinephrine – 1 μg/kg IV bolus (lower dose may also be effective); infusion, start at 0.02 μg/kg/min, may increase to 2.0 μg/kg/min
  - Isoproterenol – infusion, 0.01–2.0 μg/kg/min
- Temporary atrial pacing – transcutaneous, transesophageal, intracardiac, epicardial

Sinus node dysfunction

Sinus node dysfunction often termed sick sinus syndrome, encompasses a spectrum of disorders characterized by slow or irregular heart rates that have a variety of escape rhythms and that frequently alternate with the periods of tachycardia. The respondent's tachycardia may be atrial tachycardia, atrial flutter, or atrial fibrillation. The term tachycardia-bradycardia syndrome is frequently used to characterize this association. The surgical interventions most likely to be associated with sinus node dysfunction include extensive atrial baffling procedures, such as Mustard and Senning operations, and the Fontan procedure. The management of symptomatic patients may include pacemaker implantation, pharmacological therapy for tachyarrhythmias, atrial antitachycardia pacing (ATP), and, in some cases, transcatheter or surgical ablation.

Sinus tachycardia

Sinus tachycardia is more commonly seen in the perioperative period than sinus bradycardia. It is often the result of painful stimuli or stress, hypovolemia, anemia, medications (e.g., inotropic agents), a high catecholamine state, surgical manipulation, or fever. Sinus tachycardia can often be differentiated from pathologic supraventricular arrhythmias by its variability in rate and its normal P-wave axis. Treatment is directed at the underlying cause. Prolonged periods of sinus tachycardia may impair diastolic filling time, limit ventricular preload, and compromise systemic cardiac output. Patients at higher risk of hemodynamic compromise have substantial ventricular hypertrophy or non-compliant



Figure 22.1 *Low atrial rhythm*. Intraoperative tracing depicting a single electrocardiographic lead (lead II), arterial blood pressure tracing (ART), and central venous pressure (CVP) waveform. Note the negative P-wave morphology in the first portion of lead II, consistent with atrial activation arising from the low atrium. The second half of the recording shows a change in the P-wave morphology (positive) and a slightly faster heart rate as the atrial impulse later originates from the high atrium (likely the sinus node).

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("stiff") ventricles with associated diastolic dysfunction, such as in certain types of cardiomyopathies or obstructive outflow lesions (e.g., tetralogy of Fallot).

Junctional rhythm

Junctional rhythm is characterized by QRS complexes with a morphology identical to that of sinus rhythm without preceding P waves. This arrhythmia is thought to originate in the bundle of His. It often occurs in patients with sinus bradycardia or with sinus node dysfunction. In this rhythm, there is normal atrioventricular (AV) nodal conduction, but it is sometimes difficult to determine if the junctional beats are slightly faster than the atrial beats or there is 1 : 1 ventriculoatrial (V:A) conduction retrograde through the AV node. During surgery, this may occur as a result of cardiac manipulation and dissection around the right atrium. In addition to the ECG features described above, the arterial and venous pressure waveforms can change during junctional rhythm (Figure 22.2). The central venous pressure tracing may show a tall *a* wave, termed as *cannon a wave*, which is due to late atrial contraction against a closed tricuspid valve. An associated decrease in stroke volume and cardiac output, resulting from the absence of the normal atrial systolic contribution to ventricular filling, may manifest as a reduction in systemic arterial blood pressure. Temporary atrial pacing at 10–20 beats/min (bpm) above the junctional rate can be used to document normal AV nodal conduction, and it frequently restores AV synchrony.

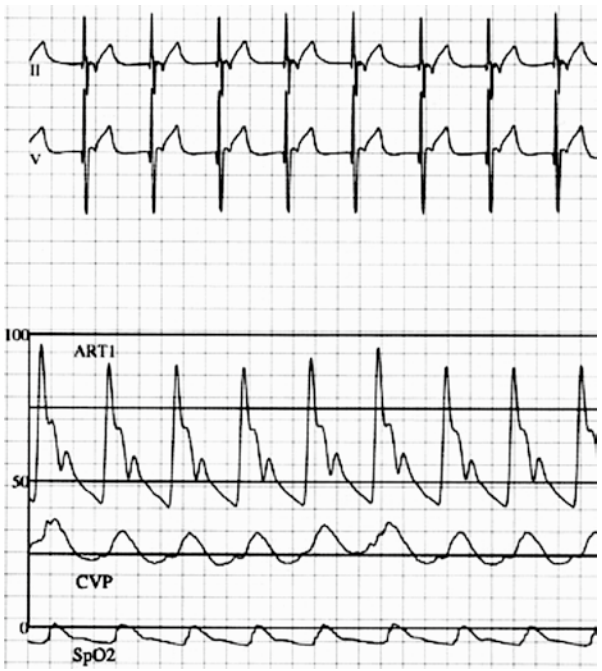


Figure 22.2 *Junctional rhythm*. Intraoperative recording showing the features of a junctional rhythm. Note the retrograde (negative) P wave after each QRS complex. The central venous pressure tracing shows prominent cannon *a* waves corresponding to right atrial contraction against increased resistance from a closed tricuspid valve. This may result in decreased ventricular filling and reduced cardiac output. ART1, systemic arterial blood pressure (scale 0–100 mmHg); CVP, central venous pressure (scale 0–60 mmHg); SpO_2, arterial oxygen saturation by pulse oximetry.

KEY POINTS: CARDIAC RHYTHM DISTURBANCES

- Sinus bradycardia may be due to vagal stimulation or drugs; it is important to exclude hypoxemia, hypothermia, hypotension, acidosis, electrolyte abnormalities, or increased intracranial pressure as potential etiologies.
- Low atrial rhythm is usually due to surgical manipulation.
- Sinus node dysfunction is more commonly seen after Mustard, Senning, and Fontan operations.
- Sinus tachycardia may be due to painful stimuli/stress, hypovolemia, anemia, medications, a high catecholamine state, surgical manipulation, or fever; treatment should be directed at the underlying cause.
- Junctional rhythm may occur due to surgical manipulation/dissection around the atrium; the central venous pressure tracing characteristically displays a tall *a* wave, and blood pressure may decrease due to loss of the atrial kick.

Conduction disorders

Bundle branch block

In an unoperated patient, bundle branch block is an uncommon ECG finding. An incomplete right bundle branch block (RBBB) pattern or intraventricular conduction delay can be seen in patients with right ventricular volume overload (e.g., ASDs, anomalous pulmonary venous drainage). In rare cases, an RBBB can be congenital and idiopathic. An RBBB pattern is frequently seen in postoperative patients after interventions for lesions such as tetralogy of Fallot, right ventricular outflow tract pathology, and AV septal defect (AVSD; also referred to as AV canal or endocardial cushion defect). This conduction abnormality may be related to a ventriculotomy incision, resection of infundibular muscle, damage to the moderator band, or, in some cases, closure of a ventricular septal defect (VSD). A left bundle branch block (LBBB) pattern is uncommon but may be found after surgical procedures involving the left ventricular outflow tract.

Atrioventricular block

First-degree AV block

First-degree AV block is characterized by a prolonged PR interval beyond what is considered normal for age. Each P wave is followed by a conducted QRS complex. This type of rhythm disturbance can be a normal variant in healthy individuals but can also be seen in a variety of disease states (e.g., structural heart defects associated with stretching of the atria, rheumatic fever). In general, a prolonged PR interval in an otherwise healthy child is a benign condition and requires no treatment.

Second-degree AV block

There are four types of second-degree AV block. The two predominant types, Mobitz type I (Wenckebach) and Mobitz type II, involve a periodic failure to conduct atrial impulses

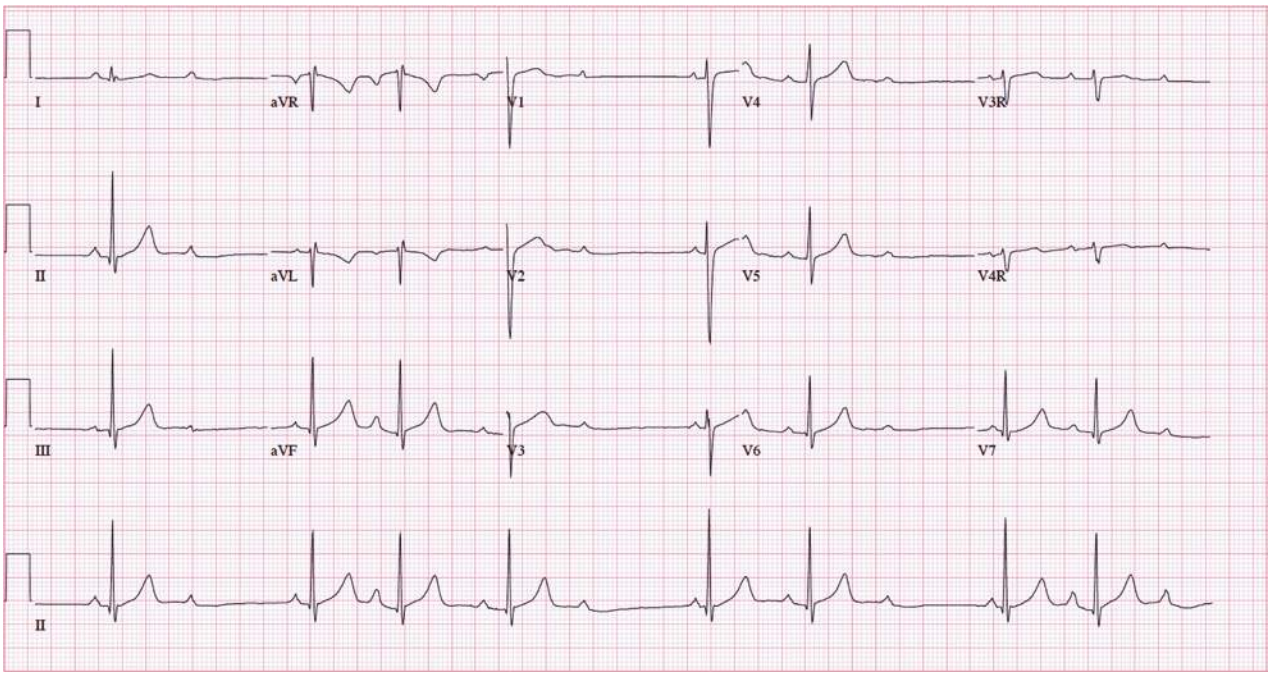


Figure 22.3 *Mobitz type I second-degree atrioventricular block (Wenckebach).* The tracing shows progressive lengthening of the PR interval and eventual failure of an atrial impulse to conduct.

to the ventricle. In *type I second-degree AV block*, the PR interval lengthens progressively until the next atrial impulse cannot be conducted to the ventricle. These failures of conduction manifest on the surface ECG as P waves without associated QRS complexes and concomitant shortening of the RR intervals (Figure 22.3). This rhythm disturbance can occur during periods of high vagal tone and is generally considered a benign phenomenon that requires no therapy.

In the less frequent *type II second-degree AV block*, there is a constant PR interval before an atrial impulse that suddenly fails to conduct. This conduction abnormality is more concerning because of its potential for progression. It can be seen in patients after surgery for CHD and is thought to be due to damage to the His bundle or distal conduction system.

The third type of second-degree AV block is *two to one AV block* (2:1). In 2:1, every second P wave is blocked. In most cases, this is a type of Mobitz type I or Wenckebach block and is secondary to high vagal tone. It is rare for 2:1 to progress to a higher degree of AV block or to require treatment.

The fourth type of second-degree AV block is a *high-grade AV block*, which is evidenced by two or more non-conducted P waves in succession that would normally be expected to conduct. Temporary pacing and close patient observation may be warranted because hemodynamically significant bradycardia or continued progression of the conduction deficit may ensue.

Third-degree (complete) AV block

Third-degree AV block is characterized by the total failure of atrial impulses to be conducted to the ventricles. There is complete dissociation of the electrical activity between the atria and ventricles, and the ventricular rate is usually slow and regular. In third-degree AV block, the ventricular escape rate may be narrow (if originating from the perinodal region) or wide (if originating from within the ventricle). The diagnostic feature on the ECG is that all atrial impulses that should be conducted to the ventricle fail to do so (Figure 22.4).

Complete AV block may be either congenital or acquired. Congenital complete AV block in infants with otherwise structurally normal hearts may be due to intrauterine exposure to maternal antibodies associated with collagen vascular diseases (e.g., lupus). Patients at high risk of complete AV block include those with congenitally corrected transposition (L-transposition of the great arteries with ventricular inversion) and those with polysplenia (left atrial isomerism) [1]. Acquired postoperative AV block is thought to result from damage to the compact AV node or bundle of His and may be transient or permanent. The surgical procedures most commonly associated with the onset of complete AV block include repair of AVSD, closure of VSD, resection of obstructive subaortic tissue, and interventions in patients with congenitally corrected transposition [2]. In children, reported incidences of surgical AV block are as high as 2–4%. Normal conduction eventually recovers in more than 60% of patients, usually within the first 10 postoperative days [3, 4]. Acute treatment includes temporary pacing (either AV sequential pacing or ventricular pacing only). If the rate of the junctional escape rhythm is high enough to support stable hemodynamics, temporary pacing can be set as a backup with close monitoring of the underlying cardiac rhythm. Important considerations in patients with surgical AV block include careful surveillance for the return of AV conduction and frequent evaluation of temporary pacing wire thresholds. The ventricular output of the temporary pacemaker should be set well above the capture threshold to increase the margin of safety (please refer to the section on temporary pacing).

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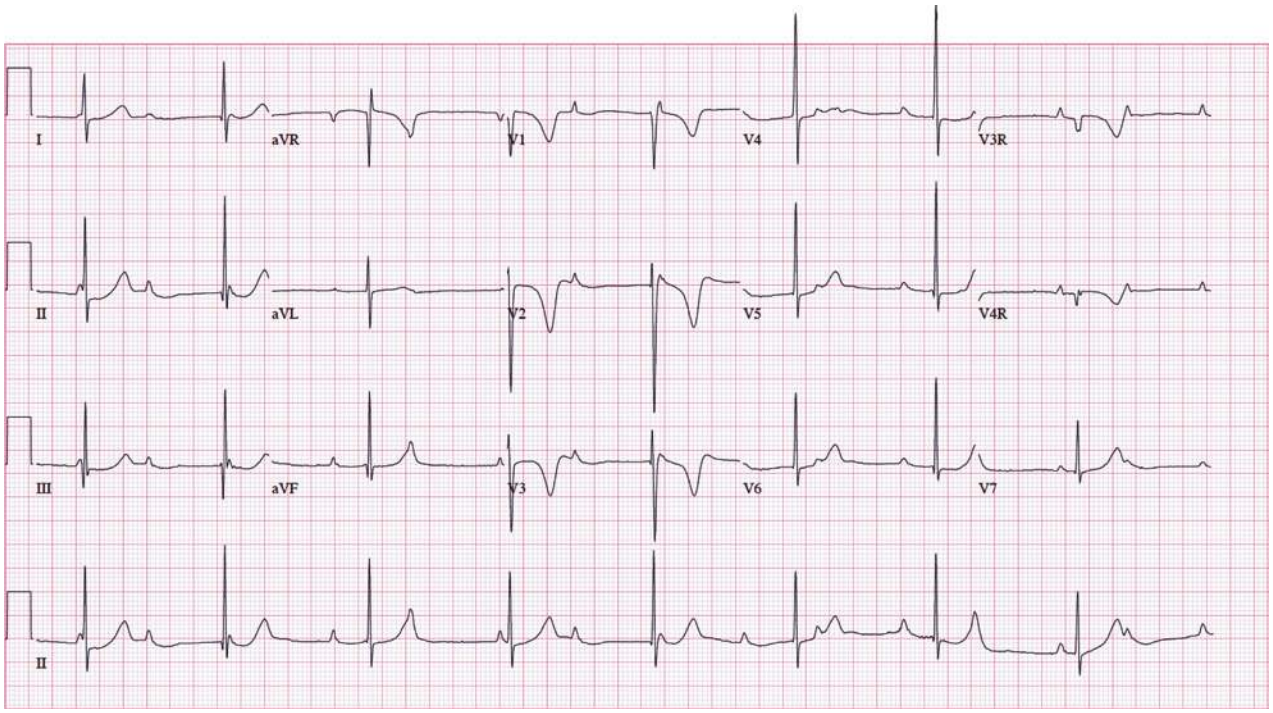


Figure 22.4 *Complete atrioventricular block*. Surface electrocardiogram showing complete dissociation between the atria and ventricles, related to inability of the atrial impulses to be propagated to the ventricular myocardium. Note that the ventricular rate is regular.

Permanent cardiac pacing is generally indicated in patients who do not recover from complete AV block within 10–14 days after surgical intervention. A small minority of patients have late recovery of their native AV nodal conduction after surgically acquired complete AV block [3, 4].

When providing anesthetic care to a patient with complete AV block but no implanted pacemaker, the following should be considered:

- *Drugs and resuscitation equipment*. Immediate availability of emergency agents such as isoproterenol and epinephrine, in addition to resuscitation equipment, is essential.
- *Transcutaneous cardiac pacing*. Equipment (pacing pads and unit) should be available in case extracardiac pacing becomes necessary. Placing the pacing pads before anesthetic induction may be prudent.
- *Access to temporary transvenous pacing*. Although insertion of a temporary pacing catheter before anesthetic care has been suggested in children with complete AV block, a retrospective study of this approach showed that using this catheter routinely had no benefit [5].

KEY POINTS: CONDUCTION DISORDERS

- First-degree AV block and Mobitz type I second-degree AV block are usually benign and do not require therapy.
- Mobitz type II and advanced second-degree AV block may progress and require pacemaker therapy.
- Patients with complete AV block with and without pacemakers require special anesthetic and surgical considerations.

Supraventricular arrhythmias

Premature atrial contractions

Isolated premature atrial contractions (PACs) are relatively common in infants and small children. The early P waves frequently have an abnormal axis and morphology and are typically followed by a normal QRS complex. Atrial bigeminy is characterized by a PAC that follows every sinus beat (Figure 22.5). On occasion, the PACs block at the AV node or conduct aberrantly, displaying an abnormally wide QRS. Blocked PACs can mimic bradycardia, and aberrantly conducted PACs can resemble ventricular ectopy. Most PACs are benign, requiring no therapy. An investigation may be warranted in cases of symptomatic, frequent, or complex (multifocal) PACs. This type of rhythm can be the result of irritation from a central venous catheter or other type of intracardiac line. Radiographic or echocardiographic assessment of catheter/wire tip position should be considered because appropriate adjustments can eliminate the atrial ectopy.

Supraventricular tachycardia

Supraventricular tachycardia (SVT) is the most common clinically significant arrhythmia in infants and children. This rhythm disturbance is characterized by a narrow or "usual" complex QRS morphology and can occur in structurally normal hearts, as well as in various forms of CHD. "Usual" complex describes a QRS morphology in tachycardia similar to that seen during normal sinus rhythm. This is important because patients with CHD often have abnormalities on their baseline ECG, including a bundle branch block pattern. On occasion, widening of the QRS duration in SVT can be due to aberrancy in the right or left bundle branches or to the



Figure 22.5 *Atrial bigeminy*. Intraoperative recording obtained from a child after creation of a Glenn anastomosis, showing a premature atrial contraction after each sinus beat during atrial bigeminy. Note that the premature atrial complexes have a different P-wave morphology from that of the sinus beats, because the premature complexes originate from a region of the atrium other than the sinus node. The variability in the arterial blood pressure shown in the tracing is due to the shortened diastolic filling time during the premature beats. ART1, systemic arterial blood pressure (scale 0–100 mmHg); LA3, left atrial pressure (scale 0–100 mmHg); PA2, pulmonary artery pressure (scale 0–100 mmHg); SpO_2, arterial oxygen saturation by pulse oximetry.

tachycardia mechanism itself (i.e., antidromic SVT; refer to the discussion later in this chapter). When the QRS complex is wide, distinguishing between supraventricular and ventricular tachycardia can be challenging.

Two general categories of SVT are recognized: *automatic and reentrant*. These can be differentiated by evaluating characteristics of the tachycardia (Table 22.1). The most common mechanisms of SVT and their ECG features are noted in Table 22.2. Evaluation of a tachyarrhythmia usually includes a surface 15-lead ECG and a continuous rhythm strip to document onset, termination, and response to medications (e.g., adenosine) or pacing maneuvers. Strips obtained from the bedside or transport monitors are helpful for determining tachycardia rate, but they are usually not sufficient for definitive diagnosis or to distinguish among tachycardia mechanisms.

Atrial electrogram

In the postoperative patient, an atrial electrogram (AEG) can be useful in both diagnosis and management of rhythm problems. This type of ECG recording is obtained from the temporary atrial wires placed toward the end of surgery (Figure 22.6). Typically, atrial wires emerge on the right side of the chest wall and ventricular wires on the left side, although this configuration may vary. Although both a standard 15-lead ECG and an AEG record the same electrical cardiac activity, these electrical sequences display distinctly different configurations in different leads. On an AEG, the P waves are larger in amplitude, making them easily recognizable because the recording is obtained from wires attached directly to the atrial myocardium. Therefore, in situations in which P waves are not clearly identified on a surface ECG, an AEG may assist in defining atrial activity and the relationship between atrial and ventricular depolarization (Figure 22.7). Such recordings can help clinicians to differentiate between atrial and junctional arrhythmias [6]. For example, during junctional tachycardia, the AEG displays P waves that are either superimposed on the R waves or dissociated from them. In most reentrant SVTs, the PR interval is longer than the RP interval, whereas in sinus rhythm, the PR interval is shorter than the RP interval. An AEG is also helpful in defining the type of an AV block if present and can facilitate the differential diagnosis of sinus node dysfunction vs. various degrees of AV block.

AEGs can be obtained from bedside monitors (Figure 22.6) or standard 15-lead ECG machines [7]. With a bedside or operating room monitor, it is best to use a rhythm strip with two or more channels so that AEG and ECG recordings can be viewed simultaneously. There are various ways to obtain an AEG along with a standard tracing, depending on various equipment-related factors (e.g., the recorder, epicardial wires, lead configuration).

The following methods of obtaining an AEG require the use of a standard 15-lead ECG machine:

- If *two atrial wires* are present, each lead is attached to the connectors that usually correspond to the right and left arm leads (an alligator clip can be used, if necessary). This allows for a bipolar AEG (large deflection of atrial depolarization with trivial or no signal representative of ventricular activity) to be recorded in lead I. The chest (precordial) leads provide ECG standard tracings. By

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Table 22.1 Characteristics of supraventricular tachycardia mechanisms

Features of the tachycardia	Automatic	Reentrant
Onset and termination	"Warm-up" at initiation, "cool-down" at termination	Abrupt
Mode of initiation	Spontaneous	Premature beats
Ability to initiate/terminate with timed premature beats	No	Yes
Variation in tachycardia rate	Wide	Narrow
Response to catecholamines	Increased rate	None or slight rate increase
Response to adenosine	None	Termination
Response to drugs that increase refractoriness	Variable	Slowing or termination
Response to overdrive pacing	Transient suppression, quick resumption	Termination
Response to cardioversion	None	Termination

Table 22.2 Mechanisms and electrocardiographic features of supraventricular tachycardia

Diagnosis	Electrocardiographic features
Automatic tachycardias	
Ectopic atrial tachycardia or atrial ectopic tachycardia	Atrial rates of 90–330 bpm Incessant rhythm From atrial focus distinct from the sinus node Abnormal P-wave morphology and/or axis Distinct P waves preceding QRS complexes No influence of AV block on tachycardia
Junctional ectopic tachycardia	Narrow QRS tachycardia Incessant rhythm AV dissociation (often) Atrial rate slower than the ventricular rate Capture beats frequently seen (QRS complexes slightly earlier than expected from antegrade conduction of normal sinus impulses)
Reentrant tachycardias	
Atrial flutter	Sawtooth pattern or more discrete undulating P waves (leads II, II, aVF) Variable rates of AV conduction seen (1:1, 2:1, 3:1, or 4:1)
Atrioventricular reentrant tachycardia (accessory pathway-mediated from concealed bypass tract or Wolff-Parkinson-White syndrome)	P waves immediately following the QRS complex, on ST segment or T wave AV block results in termination of tachycardia
Atrioventricular nodal reentry tachycardia	P waves buried within QRS and not discernible AV block results in termination of tachycardia

AV, atrioventricular

evaluating the atrial activity as displayed by the AEG (lead I) and the ventricular impulses represented by the QRS complexes on the chest leads (V1–V6), the electrical sequence of cardiac events can be assessed.

- If only a *single atrial lead* is available, this can be attached to one of the chest leads to obtain a corresponding AEG. In this case, the limb leads can be used to provide a reference for ventricular activity (Figures 22.6 and 22.7).
- An *alternate lead configuration* may utilize a single atrial lead and a skin lead as a substitute for the arm leads to obtain an atrial tracing in lead I , and other leads serve as a reference. A rhythm strip should be printed out so that the recordings can be examined.

In addition to assisting in arrhythmia diagnosis and the selection of appropriate treatment, temporary atrial wires can be used for rapid atrial pacing in attempts to terminate SVT due to reentrant mechanisms or to overdrive suppress an automatic focus.

General management principles for SVT

Management of SVT depends on the clinical status of the patient, the type of tachycardia, and the precise electrophysiologic mechanism that is causing SVT (Table 22.3). If the tachyarrhythmia is associated with significant hemodynamic compromise, emergent therapy is indicated. Synchronized

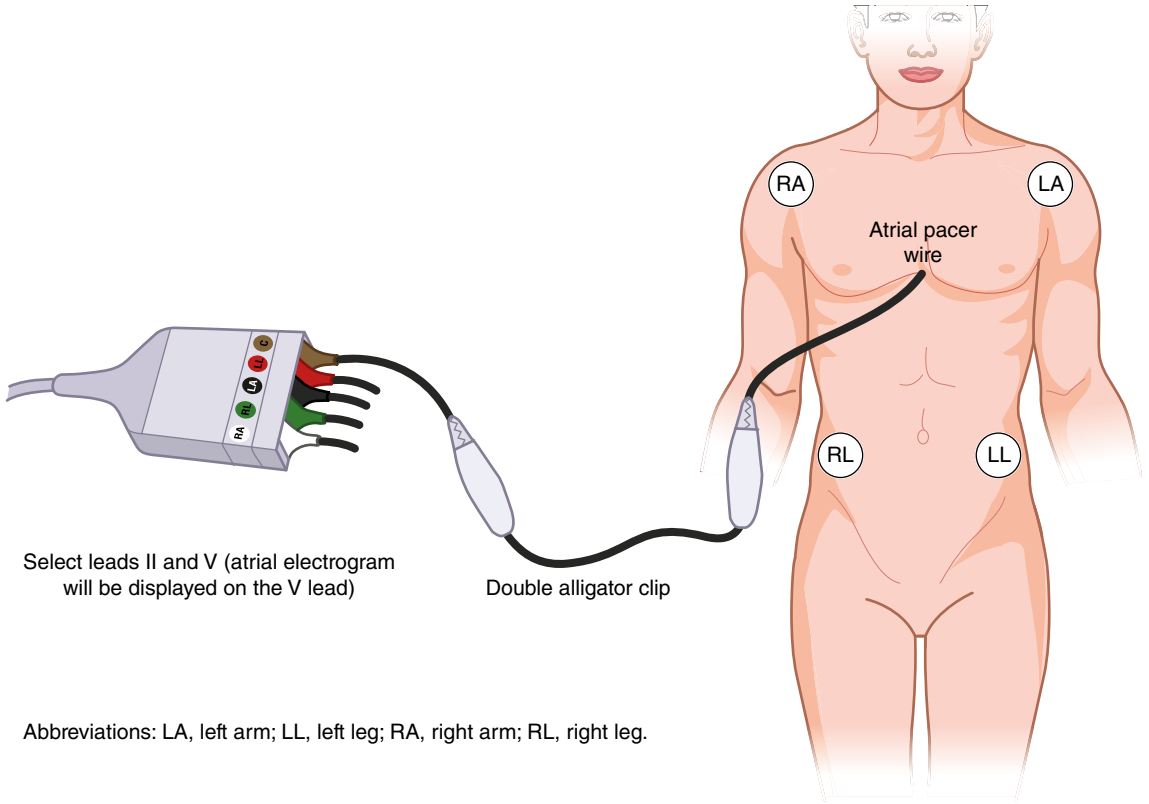


Figure 22.6 *Procedure to obtain an atrial electrogram*. Setup for recording an atrial electrogram by using a bedside (or operating room) monitor and a double alligator clamp to connect the atrial temporary pacing wire to the chest (C) or V lead (brown-colored). Alternate lead configurations may be used as described in the text to obtain equivalent tracings.

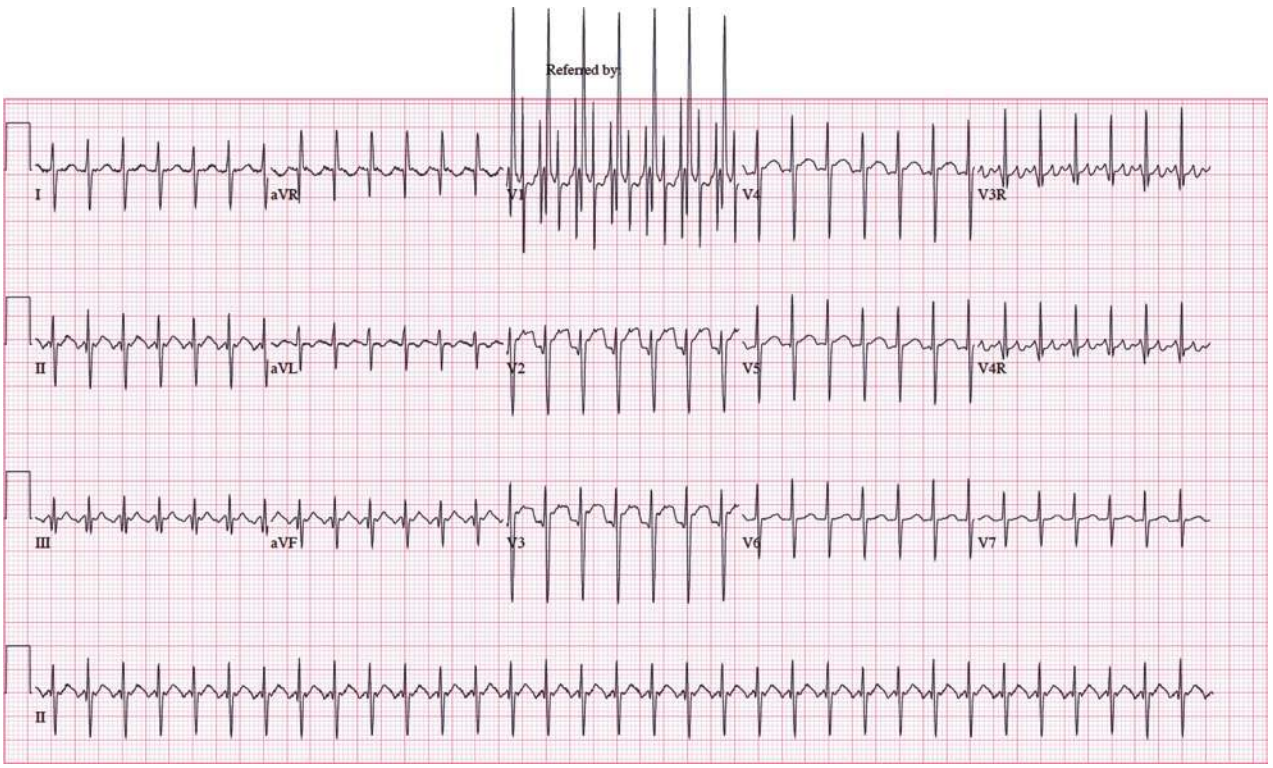


Figure 22.7 *Atrial electrogram*. Full electrocardiographic tracing with an atrial electrogram in lead V1. Note the easily discernible P waves in the atrial electrogram, which confirm that the rhythm is that of atrial flutter with 2:1 conduction.

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Table 22.3 Acute therapy of perioperative arrhythmias without evidence of hemodynamic compromise

Rhythm disturbance	Treatment considerations
Sinus bradycardia	See Box 22.1
Sinus tachycardia	Correct underlying cause
Premature atrial contractions	Evaluate the position of a central venous line or intracardiac catheter Assess/correct electrolyte disturbances (e.g., hypokalemia)
Focal (ectopic) atrial tachycardia or atrial ectopic tachycardia	Correct fever, electrolyte abnormalities Adequate sedation Consider the potential detrimental role of inotropes/vagolytics ß-blockers – use with caution if depressed cardiac function Digoxin Procainamide Amiodarone Sotalol Flecainide Propafenone Ivabradine
Multifocal (chaotic) atrial tachycardia	As in ectopic atrial tachycardia Goals are rate control and decreased automaticity
Accelerated junctional rhythm	Correct fever Consider the potential detrimental role of inotropes/vagolytics Temporary atrial pacing
Junctional ectopic tachycardia	Correct fever and electrolyte abnormalities Consider the potential detrimental role of drugs (e.g., inotropes) Adequate sedation (dexmedetomidine) Surface cooling to 34–35 °C Temporary atrial pacing (for JET rates <180 bpm) Amiodarone Hypothermia plus procainamide Sotalol Ivabradine
Atrial flutter	Adenosine to confirm the diagnosis Atrial overdrive pacing Digoxin Procainamide Amiodarone Sotalol Propafenone
Atrial fibrillation	Digoxin (except in Wolff–Parkinson–White syndrome) ß-blockers Procainamide Quinidine Amiodarone Sotalol
Atrioventricular reentrant tachycardia or atrioventricular nodal reentrant tachycardia	Consider vagal maneuvers Adenosine Atrial overdrive pacing Procainamide Amiodarone Sotalol
Premature ventricular contractions	Identify and treat underlying cause Lidocaine
Ventricular tachycardia	Lidocaine Amiodarone Procainamide Sotalol Magnesium (for *torsades de pointes*) ß-blockers Phenytoin (for digitalis toxicity)
Ventricular fibrillation	Lidocaine (adjunct to defibrillation/prevent recurrence) Amiodarone (adjunct to defibrillation/prevent recurrence)

direct-current cardioversion (0.5–1.0J/kg) should be considered for a patient with any acute tachyarrhythmia associated with low cardiac output, recognizing that this approach does not always restore normal sinus rhythm.

Atrial tachycardias

The automaticity of atrial tissue accounts for the majority of supraventricular arrhythmias in this group [8]. In general, these rhythm disorders are more recalcitrant and difficult to treat than reentrant ones.

Focal atrial tachycardia

Focal atrial tachycardia (AT) originates from a single focus in the atrium outside of the sinus node. In the past, this rhythm disturbance was thought to be due solely to enhanced automaticity. Thus, it was often referred to as an automatic or ectopic AT (EAT; also known as atrial ectopic tachycardia, or AET). In rare cases, however, focal AT is triggered or microreentrant in origin and is not due to a true ectopic focus. These forms of AT cannot be easily differentiated on the basis of the surface ECG alone. The clinical characteristics of EAT follow those outlined in Table 22.1 for automatic tachycardias. EAT may be incessant or episodic. The diagnosis is made by identifying abnormal P-wave morphology, axis, or both on a surface ECG or rhythm strip (Figure 22.8). Also, the PR interval may differ from that in sinus rhythm. Atrial rates in EAT are faster than usual sinus rates for the age and physiologic state of the patient. If the atrial rates are very rapid, some of the atrial impulses may not be conducted to the ventricles because of AV node refractoriness.

Ectopic AT is relatively rare and is generally found in two different clinical scenarios [9, 10]. A child with a structurally normal heart can develop EAT as a primary phenomenon. In older children, EAT can be incessant and, on rare occasions, lead to the development of ventricular systolic impairment or result in dilated cardiomyopathy due to the chronicity of the tachycardia. In neonates and infants, EAT often follows a more benign course and frequently resolves spontaneously early in life. A patient with CHD can also develop EAT in the postoperative period after cardiac surgery. In such cases, EAT tends to be episodic and transient, usually resolving within days. It has been reported that postoperative patients who developed EAT tended to have a lower preoperative oxyhemoglobin saturation, increased inotropic support both pre- and postoperatively, and a previous atrial septostomy [11]. No specific cardiac repair has been associated with the development of EAT.

Management principles for postoperative EAT

- *General considerations*. The management of postoperative EAT includes the treatment of fever if present, adequate sedation, correction of electrolyte abnormalities, and the withdrawal of medications that cause sympathetic stimulation (e.g., inotropic agents) or have vagolytic properties.
- *Anti-arrhythmic therapy*. The institution of pharmacologic treatment is based on overall heart rate, the duration of the tachycardia, and the hemodynamic status of the patient. Treatment relies on clinical judgment and is influenced by ventricular function. There are no large studies on antiarrhythmic drug efficacy in postoperative EAT. Medications such as esmolol, procainamide, and amiodarone can be effective in slowing the tachycardia rate [12]. Oral agents (class I, II, and III drugs) can also be of benefit. Digoxin has a minimal effect on the atrial focus but can decrease the ventricular response by slowing AV conduction [13].

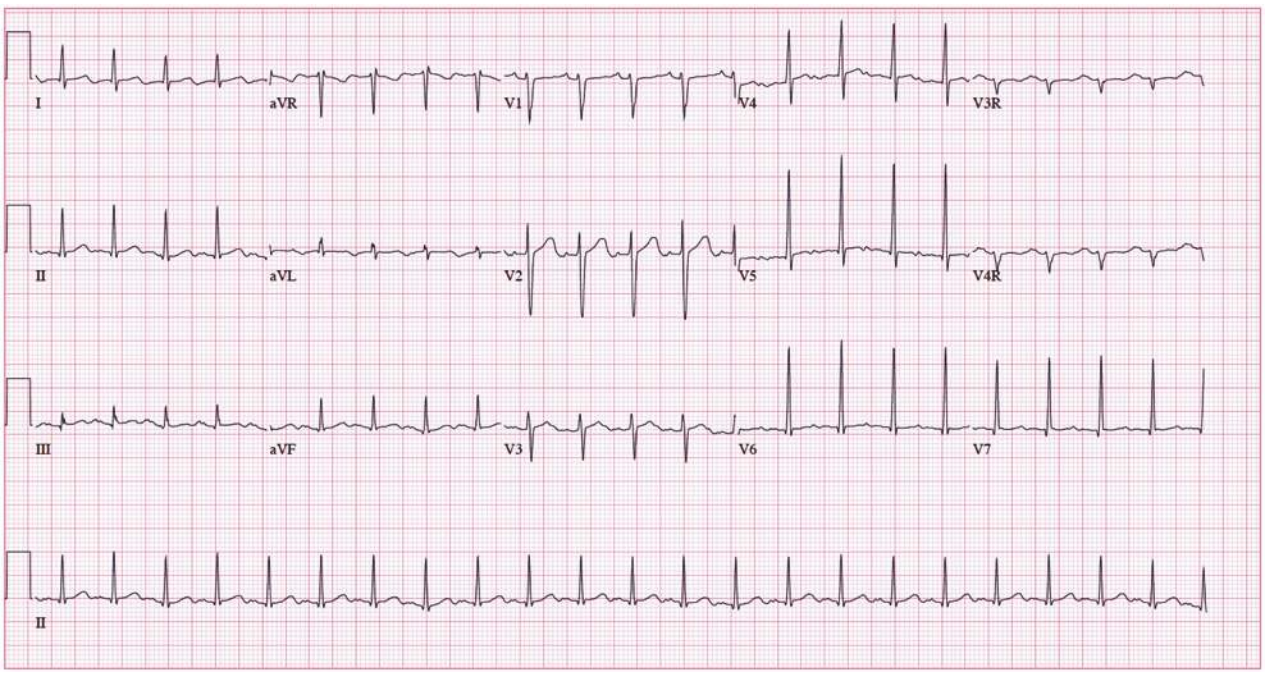


Figure 22.8 *Ectopic atrial tachycardia*. Fifteen-lead electrocardiogram in a 6-year-old child with ectopic atrial tachycardia. The characteristic features of the tachycardia are shown, including a faster-than-expected heart rate for age and an abnormal P-wave axis (left atrial focus).

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- *Ablation therapy*. In very few postoperative patients, EAT can be incessant and life-threatening, and consideration should be given to transcatheter ablation of the atrial focus [14]. It has been reported that propofol anesthesia may not be appropriate for children undergoing catheter ablation of EAT, because administering this drug may terminate the tachycardia and prevent it from being induced by isoproterenol infusion (See Chapter 34) [15].
- *Other modalities*. Atrial pacing and cardioversion are unlikely to resolve EAT.

Multifocal atrial tachycardia

Multifocal atrial tachycardia (MAT), also known as chaotic atrial rhythm, is an uncommon atrial arrhythmia characterized by multiple (at least three) P-wave morphologies [16]. These different morphologies correspond to multiple foci of automatic atrial activity. Characteristic ECG features include variable PP, RR, and PR intervals and typical atrial rates that exceed 100 bpm. MAT can be seen in young infants without structural heart disease, in postoperative CHD patients, and in children with non-cardiac medical conditions [17, 18]. Treatment focuses on ventricular rate control or decreasing automaticity, or both. Drugs such as digoxin, procainamide, flecainide, amiodarone, and propafenone have been found to be successful in converting MAT to sinus rhythm in children [19]. Adenosine, pacing, and direct-current cardioversion are usually ineffective.

Junctional tachycardias

The automaticity of junctional tissue accounts for the majority of supraventricular arrhythmias in this group [8]. These rhythm disorders tend to be somewhat resistant to standard pharmacological therapy.

Accelerated junctional rhythm

Accelerated junctional rhythm is an arrhythmia that arises from the AV junction. Characteristics of this automatic rhythm include a narrow or "usual" QRS pattern with no preceding P wave. There is either VA dissociation, with ventricular rates faster than atrial rates, or the presence of 1 : 1 VA conduction retrograde via the AV node. Temporary atrial pacing at a rate of 10–20 bpm faster than the junctional rate often re-establishes AV synchrony and effectively suppresses the automatic junctional rhythm. Changes in the patient's physiologic state (including fever), chronotropic agents, and endogenous catecholamines can stimulate the automatic junctional focus, increasing junctional rates. This rhythm is usually well-tolerated and is easily managed with temporary pacing and control of the patient's underlying physiologic state.

Junctional ectopic tachycardia

Junctional ectopic tachycardia (JET) is another automatic rhythm that arises from the AV junction. It is a narrow or "usual" complex tachycardia without preceding P waves. It is distinguishable from accelerated junctional rhythm on the basis of the patient's heart rate and hemodynamic status. This tachyarrhythmia has been classically defined by heart rates above 160 or 170 bpm with resultant hemodynamic compromise [20]. The diagnosis of JET has also been considered if the junctional rate exceeds the 95th percentile of heart rate for age [21]. There is either VA dissociation with ventricular rates faster than atrial rates or the presence of 1:1 VA conduction (Figure 22.9). If 1:1 VA conduction is identified, a trial of adenosine or rapid atrial pacing may be beneficial to differentiate JET from other reentrant forms of SVT on an AEG.

This type of tachycardia typically occurs in the immediate postoperative period and usually results in hemodynamic instability and significant morbidity and may contribute to mortality [22–24]. It occurs most commonly after surgical intervention for tetralogy of Fallot, VSD, AVSD, transposition of the great arteries, and total anomalous pulmonary venous return [25]. Other risk factors for the development of JET are long ischemic cross-clamp and cardiopulmonary bypass times, young age, and the need for inotropic support [26, 27]. Excessive retraction of tissues to allow for intracardiac surgical exposure anecdotally has also been linked to JET. Several strategies have been used to decrease the incidence of postoperative JET. The administration of magnesium during cardiopulmonary bypass decreases the incidence of postoperative JET, its use appears to be more effective in higher complexity surgeries [28, 29]. Another strategy that has shown promise in the reduction of postoperative JET is the use of dexmedetomidine in the perioperative period [30, 31].

Management principles for postoperative JET

Numerous therapies have been advocated for JET [23, 24, 26, 32]. Strategies for acute care include the following:

- *General considerations*. Core temperature cooling (to 33–35 °C) in the younger patient by the use of cooling blankets, fans, or cold compresses has been shown to be of benefit in reducing the tachycardia rate [33–35]. Shivering, if significant, should be minimized to prevent potentially detrimental increases in oxygen consumption. Additional suggested approaches include withdrawing or decreasing vagolytic agents and any medications associated with catecholamine stimulation and correcting abnormal levels of electrolytes, especially magnesium, potassium, and calcium.
- *Atrial pacing*. Temporary atrial pacing at heart rates 10–20 bpm above the JET rate establishes AV synchrony and often improves hemodynamics. However, if the JET rate is faster than 180 or 190 bpm, overdrive atrial pacing often confers a little benefit.
- *Anti-arrhythmic medications*. The two most widely used drugs for JET are amiodarone and procainamide [26, 32, 36–38]. *Amiodarone* has a longer onset of action and a longer half-life than procainamide. The drug has been shown to reduce the heart rate in JET patients during the initial bolus infusion [36, 37]. Core cooling is often continued but is not generally needed for efficacy. Administering amiodarone may be a way to avoid having to evaluate clinical signs reflecting the adequacy of cardiac output (distal peripheral perfusion, skin temperature) in a patient with hypothermia and tachycardia. Amiodarone does not directly influence ventricular function and is generally thought to cause less likelihood of hypotension during the initial bolus infusion than procainamide does. However,

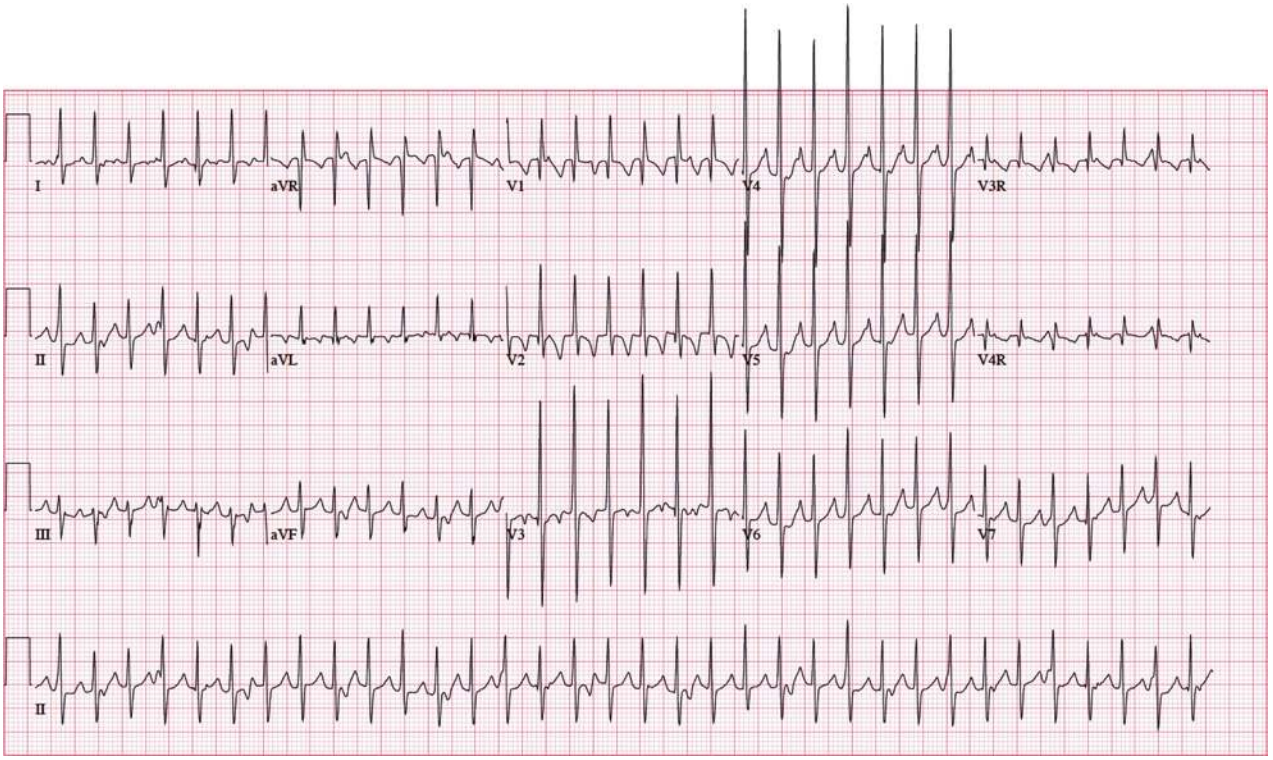


Figure 22.9 *Junctional ectopic tachycardia*. Fifteen-lead electrocardiogram in a postoperative patient with junctional ectopic tachycardia after corrective surgery for tetralogy of Fallot. The tachyarrhythmia is characterized by a narrow QRS complex and atrioventricular dissociation.

the drug should be administered with caution, given its potential adverse events (hypotension, bradycardia, AV block). The benefits of *procainamide* are that it has a faster onset of action and a shorter half-life than amiodarone. However, procainamide appears to be effective mainly when used with core cooling. It may also cause a decrease in systemic vascular resistance, with resultant hypotension, particularly during bolus infusions. Procainamide can also have negative inotropic properties. Usually, a fluid bolus or other volume expander should be given before or during procainamide therapy to maintain adequate hemodynamics. Both amiodarone and procainamide have been shown to be effective in the treatment of JET in published retrospective studies; however, the main determinant of drug selection in clinical practice is influenced by physician/institutional preference. Because amiodarone and procainamide can each cause QT prolongation and proarrhythmic side effects, these two drugs should not be administered concomitantly. Intravenous *sotalol* has been shown in case reports to be of use in the management of post-operative JET. Further studies are needed to determine the safety and efficacy of *sotalol* in the management of postoperative JET [39]. Another novel anti-arrhythmic agent that has shown promise in the management of JET is *ivabradine* (alone and in combination with amiodarone) [40–43]. *Ivabradine* is available only for oral administration, so its use is limited to patients that can tolerate oral medications. Anecdotal evidence suggests that digoxin loading can slow the JET rate, but this has not been well documented in the literature. ß-blockers and calcium-channel blockers can depress myocardial contractility, a feature that may limit their use in the immediate postoperative period. In this regard, a short-acting agent such as *esmolol* may offer a larger margin of safety. The use of intravenous (IV) class IC agents such as *propafenone* and *flecainide* has been reported, but these drugs have not been studied extensively for JET [44–46]. The natural history of perioperative JET is that it resolves within 2–5 days after the surgical intervention. Long-term anti-arrhythmic therapy is usually not necessary. Rarely, extracorporeal membrane oxygenator (ECMO) support may be necessary for incessant hemodynamically significant JET not responding to other therapies.

- *Cardioversion* is generally considered ineffective in terminating JET.
- *Catheter ablation* of the junctional focus should be considered only as a last resort, because it can result in complete AV block, given that postoperative JET is usually transient [47, 48].

Reentrant supraventricular tachycardias

Reentry, also known as "circus" movement or reciprocation, implies that a single stimulus or excitation wave front returns and reactivates the same site or tissue from which it originated. Reentrant forms of SVT may or may not involve accessory pathways.

Atrial flutter

Atrial flutter is a rhythm disturbance confined to the atrial myocardium. The electrophysiologic basis for this arrhythmia involves reentry within the atrium itself. The typical or

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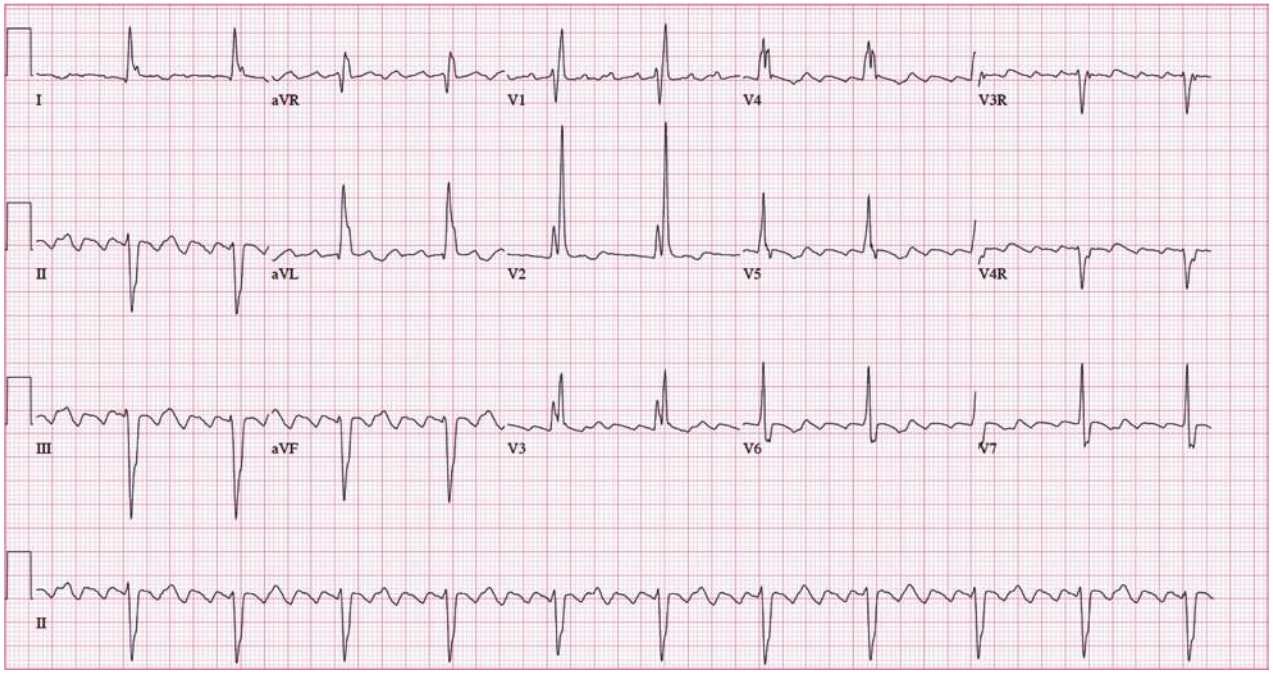


Figure 22.10 *Atrial flutter*. Surface electrogram showing the typical features of atrial flutter: sawtooth flutter waves and 4:1 atrioventricular conduction.

classic form of atrial flutter is characterized by a negative sawtooth P-wave pattern and atrial rates that exceed 300 bpm (Figure 22.10). This form of atrial flutter is occasionally seen in otherwise healthy neonates but is relatively uncommon in children. In patients with CHD, slower atrial rates and varying P-wave morphologies are more frequently seen than in those without CHD. This is due to anatomic abnormalities related to suture lines, scars, or fibrosis from a previous surgery involving atrial tissue. This form of "scar flutter" is commonly termed intra-atrial reentrant tachycardia (IART) [49]. It is one of the most common arrhythmias in postoperative patients with structural heart disease and is considered the cause of significant morbidity after certain types of surgical interventions [50]. Procedures that involve extensive atrial suture lines, such as atrial redirection procedures (Senning or Mustard operations) and those associated with atrial dilation (Fontan surgery) pose a particularly high risk of atrial flutter. The possibility of atrial flutter is suggested by the abrupt onset of a rapid atrial rhythm that remains relatively regular over time. AV nodal conduction accounts for variability in the ventricular response rate. Rapid clinical deterioration is likely; fast ventricular rates frequently require prompt intervention.

Management principles for atrial flutter

- *Adenosine* will not terminate tachycardia but may assist in confirming the diagnosis by uncovering flutter waves during AV block.
- *Atrial overdrive pacing* is a safe and effective way to rapidly terminate atrial flutter by using a transesophageal or transvenous pacing catheter or epicardial wires [51]. After the atrial cycle length is assessed, rapid atrial stimulation is performed in short bursts to attempt an interruption of the reentry circuit.
- *Synchronized cardioversion* is the treatment of choice in any patient with unstable hemodynamics. Placement of the cardioversion pads over the front and back of the hemithorax may be necessary to provide a shock vector through the entire atrium, which is usually thickened in patients with CHD.
- *Pharmacologic agents* such as digoxin, procainamide, sotalol, and amiodarone can be used in urgent situations. Drugs for controlling the ventricular response in atrial flutter include ß-blockers and calcium-channel blockers. Important considerations regarding drug selection are patient age, underlying ventricular function, and whether there is sinus node dysfunction (a concomitant problem in patients with recurrent atrial flutter). Ibutilide and sotalol are available for rapid termination of atrial flutter and have been used in postoperative pediatric and adult patients with CHD [52–55].
- *Long-term drug therapy* is frequently necessary in patients with CHD because of the potential for recurrence and associated rapid AV conduction.
- *Pacemaker therapy*, *atrial anti-tachycardia pacing*, and *radiofrequency ablation* are additional modalities often used for long-term management of atrial flutter.

Atrial fibrillation

Atrial fibrillation is a complex arrhythmia that can be due to either multiple reentrant circuits or focal points within the pulmonary veins. In the majority of cases, it originates in the left atrium (in contrast to atrial flutter, which is generally considered a disease of the right atrium). In children, this tachyarrhythmia is less frequent than atrial flutter. The atrial rates are rapid and irregular, ranging from 400 to 700 bpm. Ventricular response rates are variable but generally range between 80 and 150 bpm. Patients at potential risk for atrial

fibrillation include those with an enlarged left atrium (e.g., rheumatic heart disease, severe AV valve regurgitation), pre-excitation syndromes, structural heart disease (Ebstein anomaly, tricuspid atresia, ASDs), and cardiomyopathies.

Management principles for atrial fibrillation

- Its management principles are similar to those for atrial flutter except that atrial overdrive pacing is not effective in terminating the arrhythmia.
- *Cardioversion* is more likely to be required, and higher amounts of energy may be needed. As in the case of atrial flutter, the placement of cardioversion pads should be optimized by using a front and back configuration over the chest. Anticoagulation and consideration of transesophageal echocardiography for evaluating intracardiac thrombi are recommended before cardioversion if atrial fibrillation has been present more than 48 hours [56, 57].

Atrioventricular reentrant tachycardia and atrioventricular nodal reentrant tachycardia

Atrioventricular reentrant tachycardia (AVRT) is the most common type of SVT in infancy and childhood. It is mediated by an accessory pathway between the atrium and ventricle. The tachycardia circuit typically consists of conduction from the atrium, down the AV node, through the bundle of His and ventricles, and then up the accessory connection back to the atrium. This form of SVT is referred to as *orthodromic SVT* and occurs in patients with Wolff–Parkinson–White syndrome (WPW; Figure 22.11), concealed accessory pathways, and permanent junctional reciprocating tachycardia. In contrast, in *antidromic SVT*, conduction travels from the atrium, down the accessory connection, through the ventricles, up the AV node, and back to the atrium. The QRS complex in this form of SVT is wide. Antidromic tachycardia can occur in patients with WPW and other pre-excitation variants (Mahaim tachycardia).

Atrioventricular nodal reentrant tachycardia (AVNRT), or reentry within the AV node, is most likely in adolescents or young adults. In AVNRT, the AV node has two physiologically distinct components, designated the "slow" and "fast" AV nodal pathways. The typical form of AVNRT consists of antegrade conduction (from the atrium to the ventricle) via the slow pathway, followed by retrograde conduction (back to the atrium) via the fast pathway.

Both AVRT and AVNRT have clinical characteristics typical of reentrant tachycardia mechanisms as listed in Table 22.1. The two can often be distinguished by closely evaluating the surface ECG during sinus rhythm and tachycardia. In orthodromic AVRT, the P wave can be seen immediately after the QRS complex or in the ST segment or T wave (Figure 22.12). The reason for this P-wave location is that a set time is necessary for conduction to proceed from the ventricles through the accessory pathway back to the atrium. In contrast, in AVNRT, the P wave is buried in the QRS complex and is often not discernible (Figure 22.13). This is the case because the tachycardia circuit is within the AV node, and the atria and the ventricles are activated almost simultaneously. Patients with structurally normal hearts, as well as those with CHD, can have either AVRT or AVNRT. Ebstein malformation of the tricuspid valve is frequently associated with AVRT secondary to one or multiple accessory pathways. The accessory connections in this condition are usually right-sided. Congenitally corrected transposition can be associated with an Ebstenoid left-sided AV valve, and left-sided accessory pathways can be identified in a subset of patients.

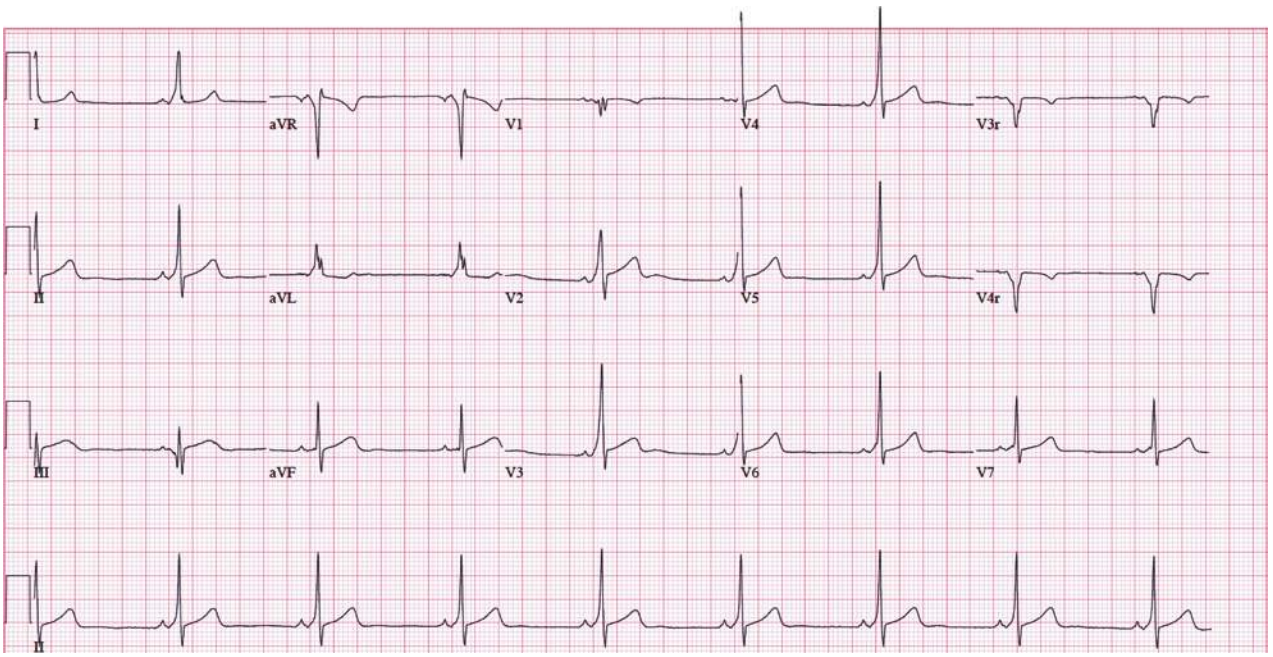


Figure 22.11 *Wolff–Parkinson–White syndrome.* Surface electrocardiogram depicting the shortened PR interval and characteristic delta wave (slurring and slow rise of the initial upstroke of the QRS complex) in the Wolff–Parkinson–White pre-excitation syndrome during normal sinus rhythm.

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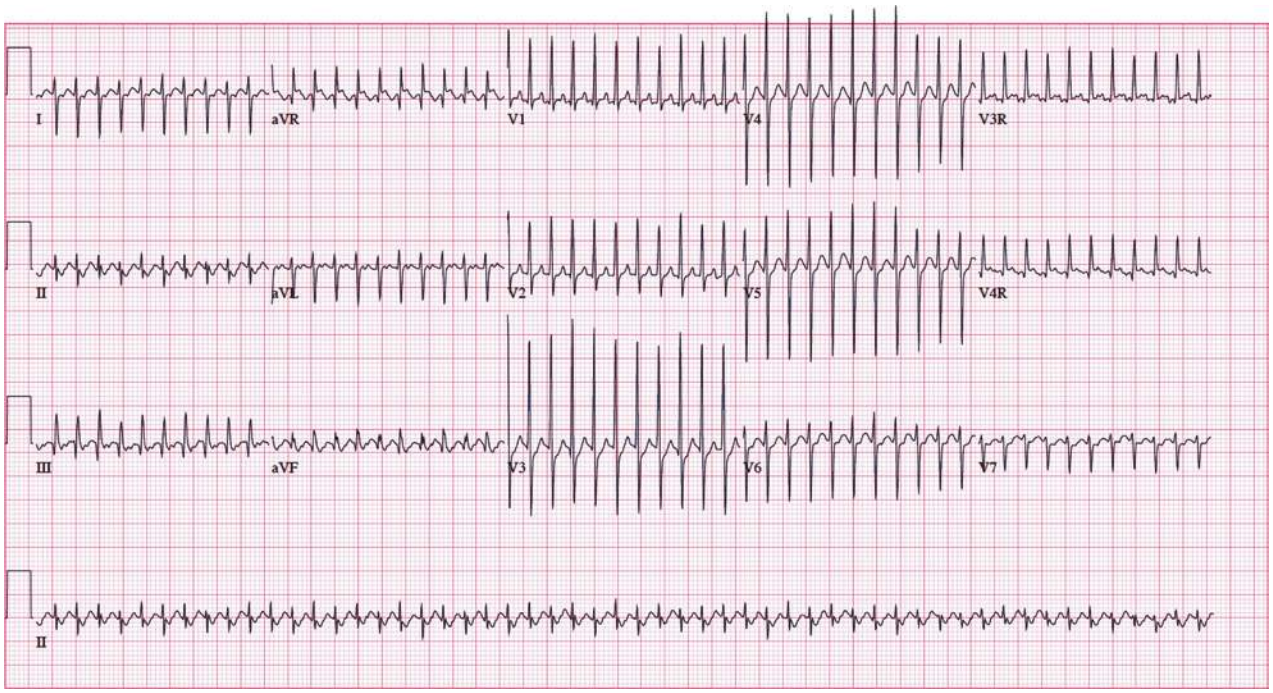


Figure 22.12 *Atrioventricular reentrant tachycardia*. Electrocardiogram showing a narrow-complex tachycardia with a regular rate and a distinct retrograde P wave approximately 80 ms after the QRS complex.

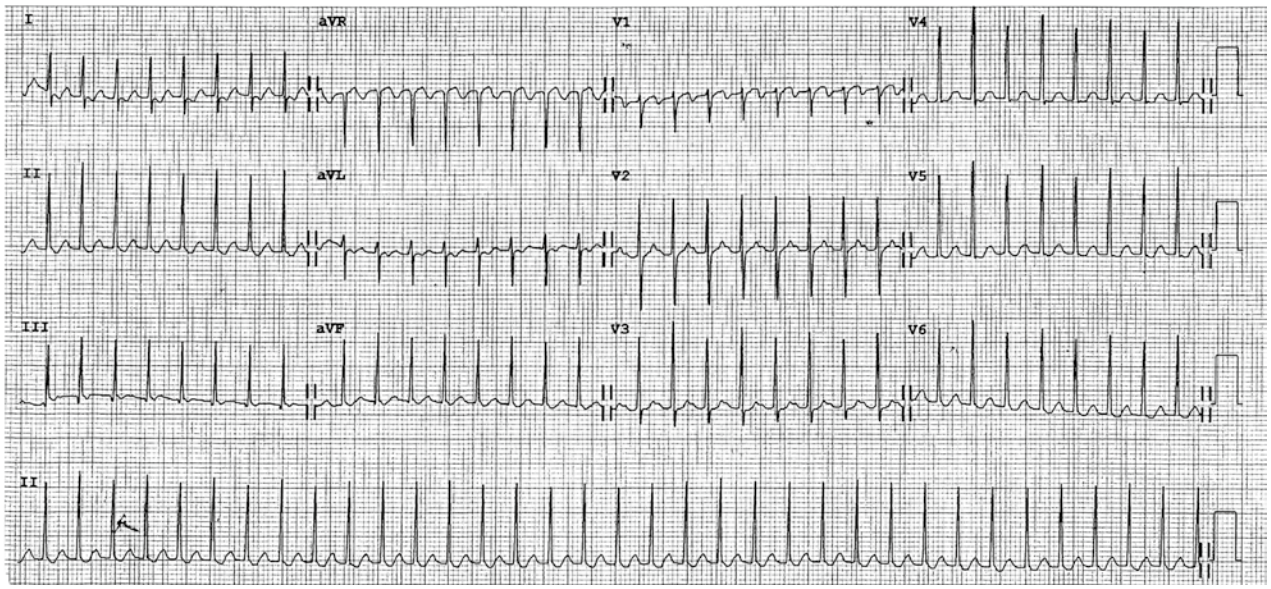


Figure 22.13 *Atrioventricular nodal reentrant tachycardia*. Electrocardiogram showing a narrow-complex tachycardia. There is no evidence of a retrograde P wave because it is obscured by the QRS complex, secondary to simultaneous atrial and ventricular activation.

Management principles for AVRT or AVNRT

- *Direct current synchronized cardioversion* (0.5–1.0 J/kg) should be performed in hemodynamically unstable patients. A lower energy setting is adequate if paddles are used directly on the heart (epicardial paddles). Cardioversion should also be considered in stable patients when potential rapid clinical deterioration is anticipated or after an unsuccessful conventional therapy.
- In stable patients, tachycardia can be rapidly terminated with *vagal maneuvers* (Valsalva maneuver, coughing, gag reflex stimulation, ice to the face, Trendelenburg position), which enhance parasympathetic influences [58].
- *Adenosine* is the first-line drug therapy for SVT [59–62]. Other agents (digoxin, edrophonium, ß-blockers, calcium-channel blockers, phenylephrine, dexmedetomidine, sotalol) have been used in acute treatment with variable

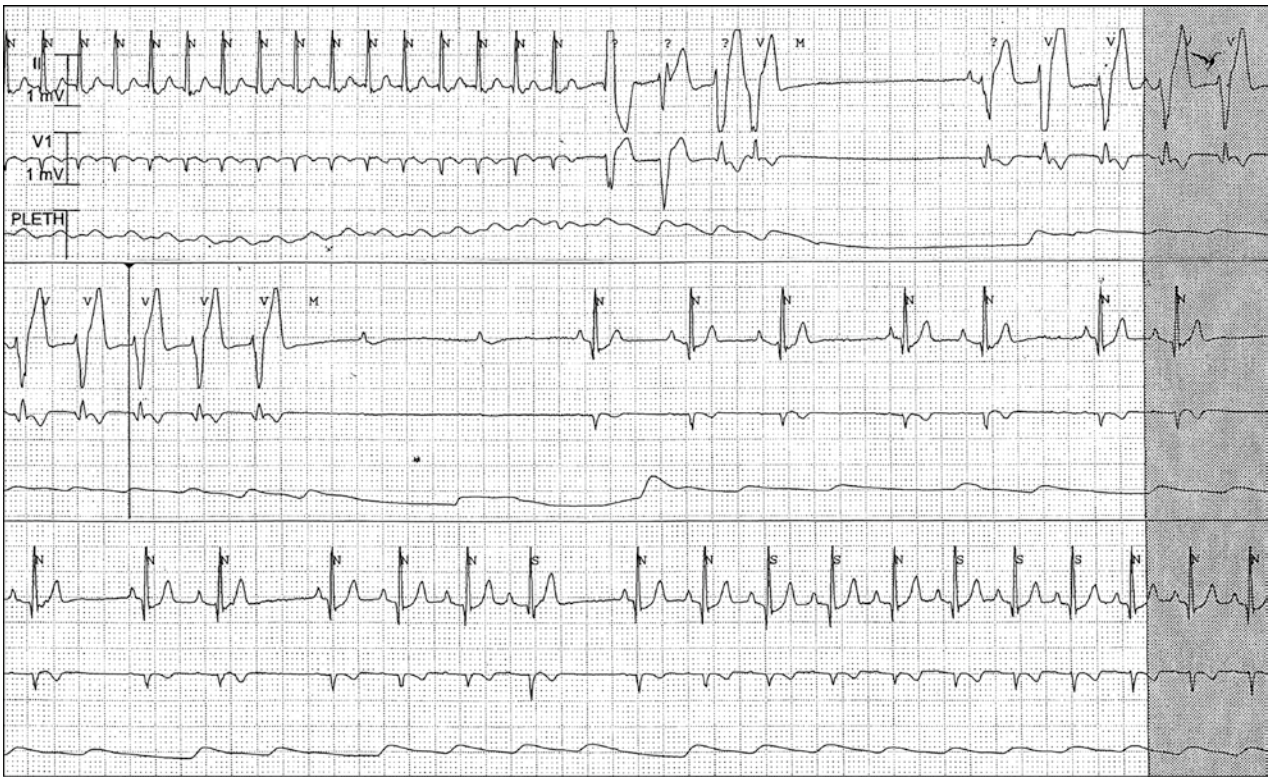


Figure 22.14 *Adenosine treatment of supraventricular tachycardia*. Tracings showing effects of an adenosine bolus administered during supraventricular tachycardia (*upper panel*). Upon termination of the tachycardia, several ventricular beats are seen (right half of upper panel), followed by just atrial beats (*middle panel*) and restoration of sinus rhythm (*lower panel*).

results; however, serious adverse effects can be seen. Continuous ECG monitoring is recommended, as well as the availability of atropine and other emergency drugs is ensured, because transient bradycardia may follow tachycardia termination (Figure 22.14). During short-term pharmacologic therapy, backup pacing may be appropriate, depending on the drug and clinical status of the patient.

- *Rapid atrial pacing* can be performed with a transesophageal electrode catheter or via temporary atrial pacing wires. Beforehand, one must ensure that there is no ventricular capture by the catheter or temporary wires at the desired output site. Rapid atrial pacing is performed by pacing the atrium at 10–20% faster than the SVT rate for a period of up to 15 seconds, which typically terminates the tachycardia. In a patient with a high catecholamine state, SVT can be successfully terminated but rapid recurrence is possible. In this case, a higher level of patient sedation and limiting catecholamine stimulation should be considered.
- *Anti-arrhythmic medication* can be instituted once the tachycardia has terminated or if it terminates and then reinitiates. For perioperative patients unable to take oral medications, parenteral therapy may include procainamide, sotalol, or amiodarone. β-blockers and calcium-channel blockers may be less desirable in such cases because of their negative effects on myocardial contractility; a short-acting agent, such as esmolol, may offer a larger margin of safety.
- *Transcatheter ablation* may be warranted in patients with a history of SVT who would prefer not to take medications, or in those with incessant tachycardia that cannot be controlled with medications. Success rates for transcatheter ablation exceed 95%.

KEY POINTS: SUPRAVENTRICULAR ARRHYTHMIAS

- Premature atrial contractions can be due to irritability from an intracardiac wire/catheter, therefore, tip position should be evaluated.
- SVT is the most common clinically significant arrhythmia in the pediatric age group; it is characterized by a narrow or "usual" complex QRS morphology.
- SVTs are categorized into automatic and reentrant types; these can be differentiated by evaluating features of tachycardia.
- Atrial electrograms facilitate the diagnostic assessment of tachyarrhythmias and can be obtained using bedside/operating room monitors or full ECG recordings.
- The management of postoperative JET includes consideration of overdrive temporary atrial pacing to restore AV synchrony, sedation, mild hypothermia, and drugs.
- Any acute rhythm disturbance requires prompt evaluation of hemodynamics.
- In the stable patient, vagal maneuvers, drug therapy, and rapid atrial pacing may be considered to terminate a supraventricular arrhythmia.

- Synchronized cardioversion is first-line therapy for unstable reentrant supraventricular arrhythmias.
- A wide QRS tachycardia should always be considered of ventricular origin until proven otherwise.

Ventricular arrhythmias

Ventricular arrhythmias are rhythm disorders that arise distal to the bifurcation of the common His bundle. These are relatively rare in young children and more common in patients with underlying genetically abnormal cardiac sodium or potassium channels and in adolescents or young adults with previously operated CHD. Patients with ventricular rhythm abnormalities may have few or no symptoms, or they may be gravely ill. Evaluation should include reviewing the medical history for findings suggestive of associated cardiovascular pathology or potential cause of the arrhythmia, analyzing the ECG, and, most importantly, assessing the hemodynamic state.

Premature ventricular contractions

Premature ventricular contractions (PVCs) are premature beats that originate in the ventricular myocardium. These are characterized by the following: premature QRS complexes not preceded by premature atrial activity; a QRS morphology that differs from that in sinus rhythm; a long QRS duration for the patient's age (a frequent but not universal finding); and abnormalities of repolarization. In patients with a structurally normal heart, PVCs of a single QRS morphology (uniform) without associated symptoms are generally considered benign. Premature ventricular contractions that merit further investigation include those that have multiple morphologies (multiform) on ECG, occur with moderate frequency, and are associated with symptoms or occur in a patient with an abnormal heart.

Ventricular ectopy in the perioperative period can be secondary to myocardial irritation from intracardiac catheters or direct surgical stimulation. Additional causes include respiratory (hypoxemia), electrolyte (hypokalemia), and metabolic derangements (acidosis). Isolated PVCs can also be due to pharmacologic agents (e.g., recreational drugs), myocardial injury, poor hemodynamics, and prior complex surgical intervention.

Ventricular tachycardia

Ventricular tachycardia (VT) is defined as three or more consecutive ventricular beats occurring at a rate greater than 120 bpm in adults, or more than 20% greater than the preceding sinus rate. The QRS morphology in VT is different from that in sinus rhythm and is usually wide for the patient's age. Electrocardiographic features that support this diagnosis include AV dissociation; intermittent fusion (i.e., a QRS complex of intermediate morphology occurring between two other QRSs with distinctly different morphologies); QRS morphology of VT similar to that of isolated PVCs; and tachycardia rate in children usually below 250 bpm. An RBBB QRS morphology is most common in infants with VT, whereas in older children, an LBBB pattern is more frequent with wider QRS morphologies.

Various qualifiers have been proposed to further characterize VT. The classification of VTs as monomorphic (one QRS morphology) or polymorphic (multiple QRS morphologies) is based on the evaluation of the QRS pattern in multiple ECG leads. VT is considered to be sustained or non-sustained if it lasts more or less than 30 seconds, respectively.

Acute onset of VT in pediatric patients may be due to hypoxia, acidosis, electrolyte imbalance, or metabolic problems. In the perioperative or immediate postoperative setting, the onset of VT can suggest myocardial ischemia or coronary artery injury, or both. This arrhythmia can also occur in patients with depressed myocardial function, poor hemodynamics, prior surgical interventions, myocardial tumors, cardiomyopathies (hypertrophic, dilated, left ventricular non-compaction, arrhythmogenic right ventricular dysplasia), myocarditis, acute injury (trauma), and primary sodium or potassium channel abnormalities (long QT syndrome, Brugada syndrome; see sections that follow). Among patients with CHD and ventricular arrhythmias, those at higher risk include older patients who have undergone tetralogy of Fallot repair and individuals with significant residual hemodynamic abnormalities. In patients with structural heart disease, the following potential causes of ventricular ectopy have been proposed: inadequate myocardial protection during the surgical procedure, chronic pressure or volume loads, residual or recurrent pathology, and scar formation at the ventriculotomy site.

Monomorphic VT

Although occasionally seen in patients with otherwise normal hearts, monomorphic VT is more common in those with underlying cardiac abnormalities. In the abnormal heart, tachycardia is thought to originate from a reentrant focus in scarred or damaged myocardial tissue. The ECG findings include a wide regular QRS rhythm of uniform morphology (Figure 22.15).

Polymorphic VT

Torsades de pointes

Torsades de pointes, or torsades ("twisting of the peaks"), refers to a form of polymorphic VT. The characteristic ECG feature is a varying QRS morphology manifested as positive and negative oscillations of the QRS direction that twists around an isoelectric baseline (Figure 22.16). Polymorphic VT may occur in long QT syndromes, can be secondary to drug therapy or neurologic pathology, or can result from myocardial ischemia. Torsades may terminate spontaneously or degenerate into ventricular fibrillation (VF).

Long QT syndromes

Long QT syndrome (LQTS) is an electrical disturbance that affects ventricular repolarization and predisposes children to arrhythmias such as *torsades de pointes*, VT, VF, and bradyarrhythmias [63–65]. The disorder is associated with a propensity for syncope, cardiac arrest, and sudden death.

LQTS can be congenital (inherited) or acquired. The congenital varieties are predominantly the result of genetic defects in the sodium or potassium channels responsible for maintaining electrical homeostasis in the heart. The

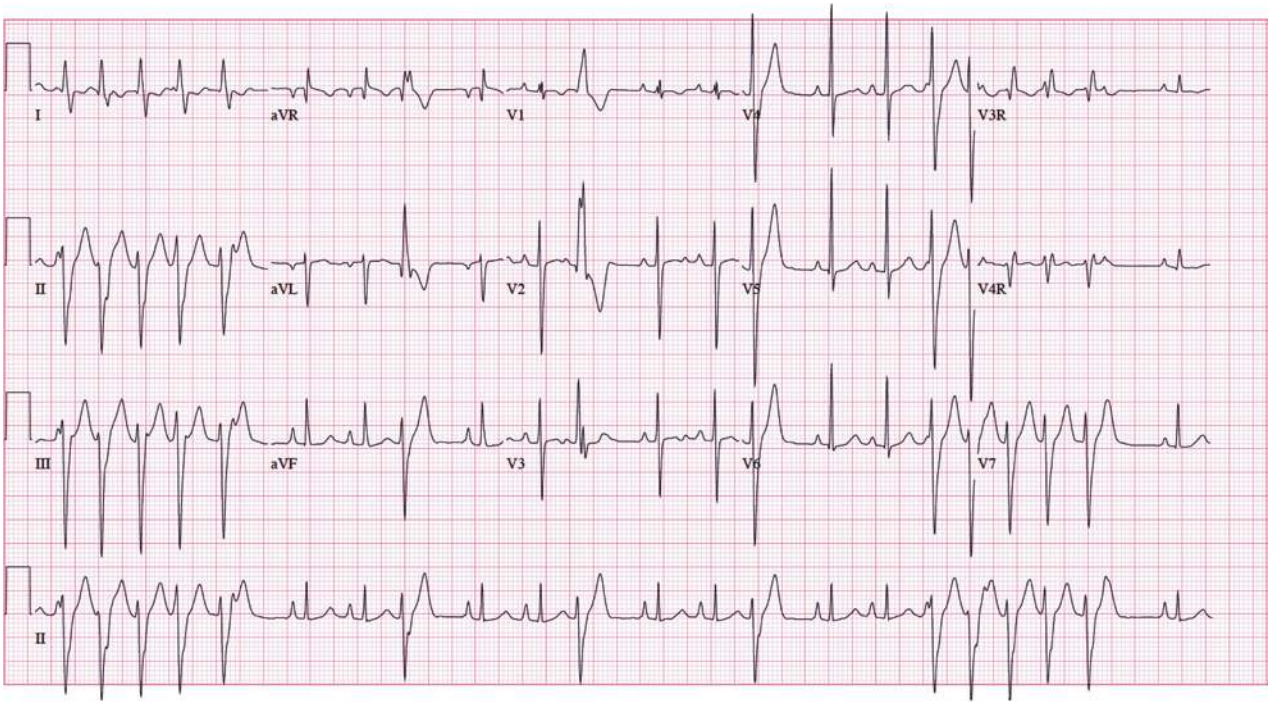


Figure 22.15 *Monophorphic ventricular tachycardia*. Electrocardiogram showing runs of a uniform wide-complex rhythm consistent with non-sustained ventricular tachycardia. The runs are separated by a few beats of normal sinus rhythm.

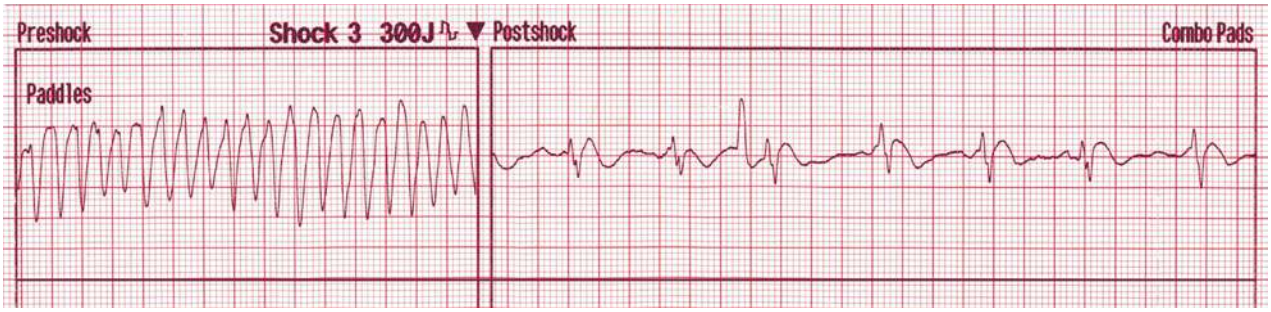


Figure 22.16 *Torsades de pointes*. The typical positive and negative oscillations of the QRS complexes in torsades are shown in this tracing (left panel). Because the arrhythmia was sustained and associated with significant hemodynamic compromise, cardioversion was performed, which terminated the tachyarrhythmia (right panel).

incidence of LQTS is not clearly known, but it is estimated that one in 5,000 individuals are gene carriers of the congenital form. The autosomal dominant variety, Romano–Ward syndrome, represents the most common form of congenital LQTS. The Jervell and Lange–Nielsen syndrome has an autosomal recessive pattern of inheritance and, in addition to QT prolongation, is characterized by deafness. Genetic testing is commercially available for LQTS-causing defects. Although efforts to develop gene-specific therapy are underway, all patients with LQTS are treated similarly at present.

Suggested clinical diagnostic criteria for LQTS are based on ECG findings, clinical history, and family history [66]. The hallmark of the disorder is the prolongation of the corrected QT interval (QTc) on the resting ECG (Figure 22.17). It should be noted, however, that individuals with LQTS may not display the repolarization abnormality manifested as QT interval prolongation. Several equations can be used to determine the QTc, the most common one being Bazett's formula:

$$\text{Corrected QT} = \text{measured QT interval} / \text{square root of preceding RR interval}$$

A QTc >0.47 seconds is considered abnormal regardless of the patient's age.

Management principles in LQTS

- *ß-adrenergic blockade*. An important aspect of perioperative management is ensuring adequate ß-adrenergic blockade and minimizing sympathetic stimulation, because this may trigger tachyarrhythmias. Premedication

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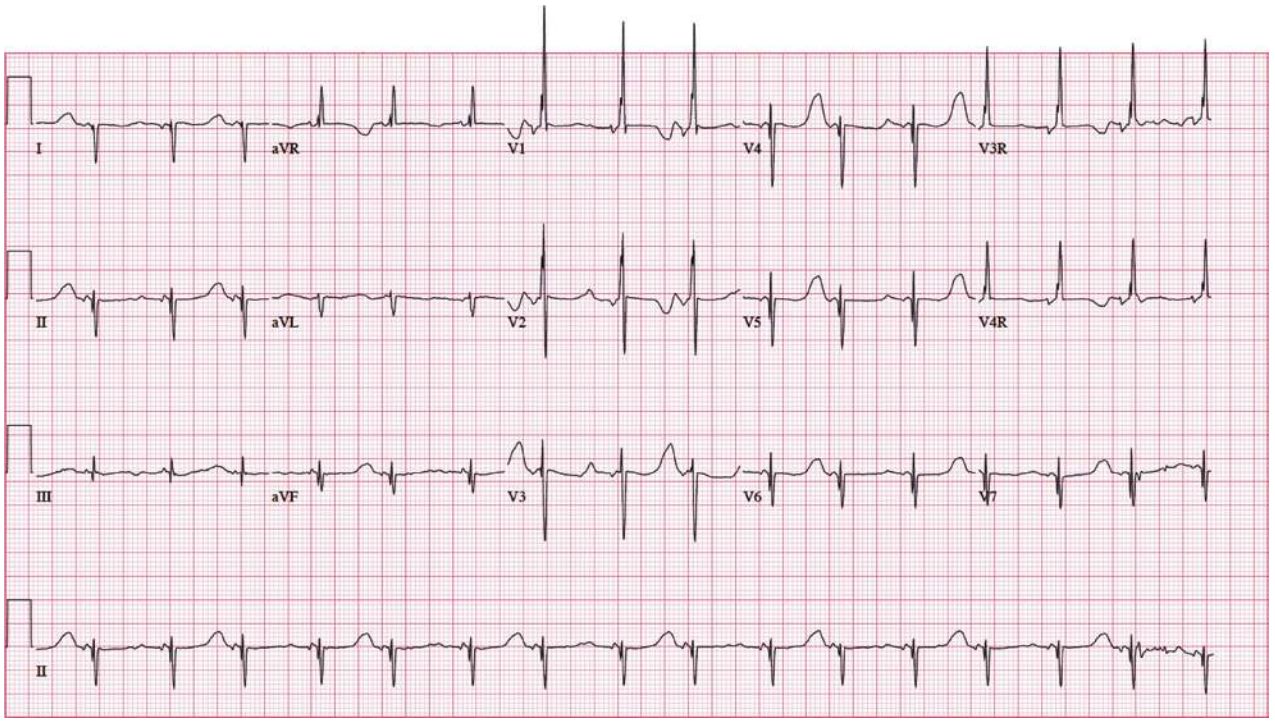


Figure 22.17 *Long QT syndrome*. Electrocardiographic recording from a child with long QT syndrome. The corrected QT interval is 0.58 seconds. Note the presence of T-wave alternans (alternating T-wave morphologies), a classic but uncommon finding in patients with long QT syndrome.

with midazolam can minimize anxiety and pain, which can also trigger arrhythmias.

- *Perioperative management*. Conditions and drugs associated with QT interval prolongation should be avoided [67]. Electrolyte abnormalities (e.g., hypokalemia, hypocalcemia, hypomagnesemia) should be corrected before surgery. Intravenous lidocaine (1.5 mg/kg) given before laryngoscopy and intubation has been shown to prevent QT prolongation that can be seen during the time of airway instrumentation and can be considered [68]. Intraoperative tachyarrhythmias can be treated with additional doses of ß-blockers and magnesium. Other beneficial drugs include phenytoin and lidocaine. Although several agents routinely used in anesthetic practice increase the QT interval (IV medications and volatile agents), in most cases these drugs are administered without untoward effects. Care should be taken in managing postoperative nausea because some antiemetics can cause QT prolongation and can increase the risk of arrhythmias. A study in children with LQTS documented an increased risk of adverse events (2.6%) during anesthetic emergence in those who received both neuromuscular blockade reversal drugs anticholinergic/anticholinesterase medication) and ondansetron. One event was described as torsades and was treated successfully [69]. These observations suggest an increased vulnerability during periods of enhanced sympathetic activity (emergence) and after the administration of drugs associated with QT interval prolongation. A comprehensive list of drugs that prolong the QT interval or may induce torsades can be found in the frequently updated and highly valuable website of The Arizona Center for Education and Research on Therapeutics (https://crediblemeds.org/index.php/login/dlcheck).
- *Postoperative care*. Patients should be closely monitored until they emerge from anesthesia and their QTc returns to preoperative values. Adequate pain control should be provided to minimize adrenergic responses that can trigger arrhythmias.

Acquired forms of long QT may result from electrolyte disturbances (hypokalemia, hypocalcemia, hypomagnesemia), drug therapy (anti-arrhythmic agents, antipsychotic drugs), and neurologic or endocrine abnormalities. Therapy in such cases should focus on correcting the underlying cause.

General management principles for VT

- A wide QRS tachycardia should always be considered to be of ventricular origin until proven otherwise, although some atypical forms of supraventricular arrhythmias may mimic VT.
- A critical aspect of caring for patients with an acute ventricular rhythm abnormality is promptly evaluating their hemodynamics. In general, sustained ventricular arrhythmias are poorly tolerated and deserve immediate attention. Unstable patients require cardiopulmonary resuscitation and electrical cardioversion.
- Pharmacological therapy may be indicated in stable patients to treat VT or to prevent its recurrence. Recommended agents include amiodarone, lidocaine, procainamide, sotalol, and ß-blockers. The choice of an agent depends on the associated clinical scenario.

- Electrical cardioversion in *torsades de pointes* should be performed only if the arrhythmia is sustained. In patients with frequent but non-sustained runs of torsades, cardioversion is of no benefit and may be detrimental. Magnesium sulfate is considered the first-line drug and lidocaine may also have a role in therapy. Procainamide and amiodarone are relatively contraindicated because they can cause QT prolongation.
- Pacing and isoproterenol may be considered for polymorphic VT associated with acquired QT prolongation such as that related to the proarrhythmic effects of certain drugs, particularly in the setting of long pauses in the cardiac cycle.

Brugada syndrome

Brugada syndrome (BrS) is a genetically determined disease characterized by a distinct ECG pattern (RBBB with coved- or saddle-shaped ST elevation in leads V1–V3) (Figure 22.18) [70]. Various genetic defects that lead to abnormalities in sodium and calcium currents have been identified in affected patients [71]. The inheritance pattern is usually autosomal dominant, although there is vast genetic heterogeneity. The genetics of this condition has been linked to phenotype severity [72]. This syndrome has rarely been reported in children [73]. It had been shown that infants with rapid VT and conduction abnormalities, but no cardiac or metabolic abnormalities, are likely to have disease-causing mutations in genes for the cardiac depolarizing channels in regions with BrS [74].

Clinically, the importance of BrS is related to its strong propensity for ventricular arrhythmias. It is thought to be responsible for 5–20% of all sudden deaths in people with structurally normal hearts. It probably remains underdiagnosed and has a national prevalence of approximately 5 in 10,000 individuals. The ECG features are often concealed or transient. In patients with suspected BrS and a normal ECG pattern, administering a sodium-channel blocker can unmask the classic pattern. Anti-arrhythmic medications appear to have limited efficacy in preventing recurrences of ventricular arrhythmias and prolonging survival in patients with BrS. Only patients with implantable cardioverter-defibrillators (ICDs) appear to be protected from sudden death. A promising new therapeutic option for patients with BrS is the possibility of epicardial ablations in the region of the right ventricular outflow tract. Epicardial ablations have been shown to eliminate the ECG findings in BrS as well as ventricular arrhythmia inducibility at the time of the study. Further data are needed to determine whether epicardial ablations prevent ventricular arrhythmias in the long term. This can potentially decrease the need for ICD in this patient population [75–77]. From the standpoint of anesthetic care, it is of note that many events in patients with BrS occur during rest or sleep, implicating sedation and

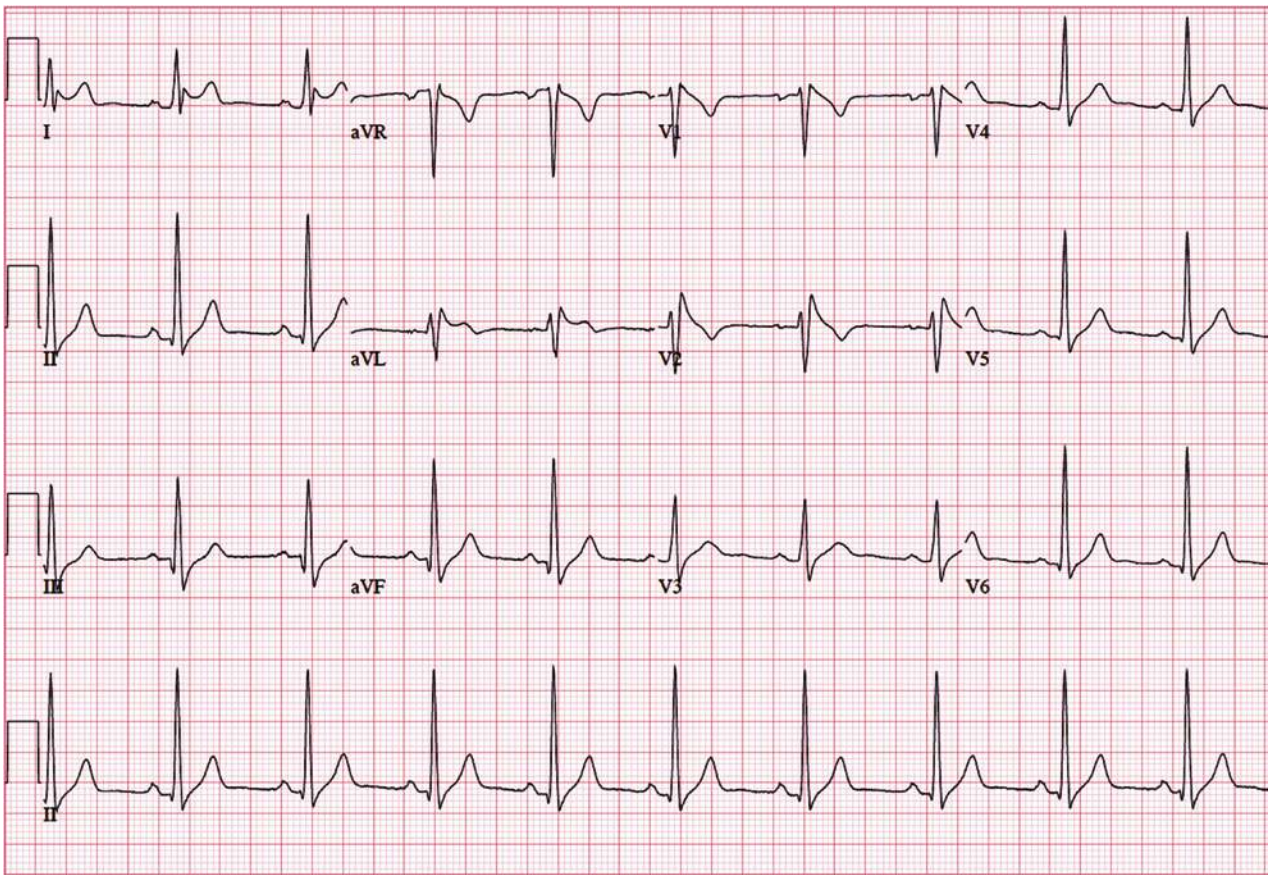


Figure 22.18 *Brugada syndrome*. Surface electrocardiogram from a child with Brugada syndrome. Note the characteristic findings of right bundle branch QRS morphology and ST-segment elevation in the right precordial leads.

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anesthesia as the time of risk. Perioperative considerations also include factors associated with further intraventricular conduction delay or ST-segment elevation potentially leading to arrhythmias (drugs, electrolyte abnormalities, and fever) [78]. In particular, sodium channel blockade should be avoided. For an updated list of drugs to be avoided in BrS, refer to www.brugadadrugs.org.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac channelopathy characterized by polymorphic VT triggered by adrenergic stimulation. It can be caused by a mutation in the ryanodine receptor 2 (*RYR2*) or in the cardiac calsequestrin (*CASQ2*) genes. It has an incidence of approximately 1 in 10,000. It usually presents as syncope precipitated by exercise, but it can also present as sudden death. Pharmacological therapy is provided primarily with ß-blockers, particularly nadolol [79]. Several studies have also shown benefits from using flecainide in conjunction with ß-blockade [80–82], and currently, many patients are started on dual therapy. In select patients, the placement of an ICD may be warranted. This form of therapy has to be used judiciously because shocks can trigger an electrical storm secondary to the adrenergic surge that follows a discharge. Left cervical sympathetic denervation can be considered in patients who are not able to tolerate ß-blockers, who have recurrent arrhythmias despite maximal medical therapy, or who meet the criteria for ICD placement but in whom ICD cannot be placed [83].

Management principles for CPVT

Adrenergic surges. Patients undergoing surgical procedures or other interventions associated with a high level of stimulation have special considerations. Extreme care should be taken to minimize adrenergic surges because the latter can trigger ventricular arrhythmias in such patients. Adequate anxiolysis and pain control should be achieved during any surgical or nonsurgical procedure that may be stimulating.

Ventricular fibrillation

VF is an uncommon arrhythmia in children. It is characterized by chaotic, asynchronous ventricular depolarizations that fail to generate an effective cardiac output. The ECG in VF shows low-amplitude, irregular deflections without identifiable QRS complexes. A loose ECG electrode may mimic these surface ECG features; therefore, immediate clinical assessment of cardiac output (i.e., checking for a pulse) should be performed and adequate ECG pad contact ensured when VF is suspected.

Management principles for VF

- *Immediate defibrillation* (initial dose of 2–4 J/kg for the transthoracic approach) is the definitive therapy because VF is lethal if left untreated. If the first shock is unsuccessful, a second shock should be delivered at double the energy dose. Infant paddles are generally recommended for those weighing less than 10 kg. Adult paddles are suggested for children weighing over 10 kg in order to reduce impedance and maximize current flow.
- *Adequate airway control* (*oxygenation*, *ventilation*) *and chest compressions* should be rapidly instituted during preparation for defibrillation or between shocks if several defibrillation attempts are needed.
- *Adjunctive pharmacologic agents* for VF include amiodarone and lidocaine. The American Heart Association's current guidelines for cardiopulmonary resuscitation and emergency cardiac care recommend using amiodarone or lidocaine as the first-line anti-arrhythmic drugs for refractory shock, pulseless VT, and VF [62, 84, 85].
- *Additional therapies* such as mechanical circulatory support should be considered.

The most widely accepted management strategies for perioperative ventricular rhythm disturbances without associated hemodynamic compromise are summarized in Table 18.3.

KEY POINTS: VENTRICULAR ARRHYTHMIAS

- Premature ventricular contractions of uniform QRS morphology are generally benign in the structurally normal heart and in asymptomatic patients; however, they may also result from myocardial irritation or other serious causes.
- VT is characterized by QRS morphology that is different than that in sinus rhythm and is usually wide.
- VT requires prompt evaluation of hemodynamic status, as it may rapidly convert to VF, resulting in cardiac arrest.
- In LQTS, perioperative ß-blockade is essential and although caution must be exercised with drugs and conditions that prolong the QT, in most cases anesthetic management is uneventful.
- VF requires the institution of cardiopulmonary resuscitation and immediate defibrillation; a loose ECG electrode should be excluded.

Pharmacologic therapy of cardiac arrhythmias

Anti-arrhythmic drugs exert their effects primarily by blocking sodium, potassium, or calcium channels, or by altering the adrenergic tone. These drugs are generally classified according to their presumed mechanisms of action and electrophysiologic effects. The well-known drug classification scheme introduced by Vaughan Williams (Table 22.4) and modified over the years is frequently used [86]. Although an oversimplification, this classification may help predict response to therapy. Appropriate drug selection requires an understanding of the mechanism of the arrhythmia and the putative effects of the agent. This section discusses pharmacologic therapy for arrhythmias, focusing on the agents that are most frequently used for acute management in children (Table 22.5) [87]. It is emphasized that perioperative consultation with a specialist

Table 22.4 Classification of anti-arrhythmic agents

Class and action	Drugs
Class I: sodium-channel blockers. Drugs may be subclassified into IA, IB, and IC categories	
IA agents – moderately depress phase zero upstroke of the action potential, slow conduction, and prolong repolarization. Effectively slow conduction in atria, ventricles, and accessory connections	Procainamide Quinidine Disopyramide
IB agents – shorten action potential duration and result in minimal alteration of conduction. These agents are usually not effective in the treatment of supraventricular tachycardia	Lidocaine Mexiletine Phenytoin
IC agents – significantly depress phase zero upstroke, with marked slowing of conduction but little change in refractoriness	Flecainide Propafenone
Class II: β-adrenergic receptor blockers. Anti-arrhythmic effects result from slowing conduction and decreasing automaticity, particularly in the sinoatrial and atrioventricular nodes	Esmolol Atenolol Metoprolol Propranolol
Class III: potassium-channel blockers. Primarily prolong action potential duration, with resultant prolongation of refractoriness	Amiodarone Sotalol Bretylium Ibutilide
Class IV: calcium-channel blockers with predominant sites of action in the sinoatrial and atrioventricular nodes.	Verapamil Diltiazem
Others	Atropine Digoxin Adenosine Ivabradine Magnesium sulfate

Table 22.5 Intravenous anti-arrhythmic agents

Agent	Dosing	
Adenosine		100 μg/kg rapid bolus, increase by 50 μg/kg every 2 minutes, up to 300 μg/kg maximum
Amiodarone	Load	5 mg/kg over 30–60 minutes
	Infusion	5–10 μg/kg/min
Digoxin	Load	20–30 μg/kg (divide as 1/2, 1/4, 1/4 every 8 hours), dose is age-dependent
	Maintenance	7–10 μg/kg/day divided every 12 hours orally
Diltiazem	Load	0.25 mg/kg up to 20 mg bolus over 2 minutes
	Infusion	0.1–0.3 mg/kg/hr, may increase up to 15 mg/hour
Esmolol	Load	500 μg/kg over 1–2 minutes
	Infusion	50 μg/kg/min starting dose, may increase gradually to 400 μg/kg/min
Flecainide (not available in the United States)		1–2 mg/kg over 5–10 minutes
Magnesium sulfate		25–50 mg/kg (up to 2 g) over 20–30 minutes
Lidocaine	Load	1 mg/kg every 5 minutes up to three times
	Infusion	20–50 μg/kg/min
Phenytoin		1–3 mg/kg over 10–15 minutes
Procainamide	Load	10–15 mg/kg over 30 to 45 minutes
	Infusion	40–50 μg/kg/min
Propafenone (not available in US)	Load	1 mg/kg over 10 minutes
	Infusion	4–7 μg/kg/min
Propranolol		0.05–0.15 mg/kg over 5 minutes
Sotalol	Load	1 mg/kg over 1 hour or 30 mg/m^2 over 15–30 minutes
	Infusion	120 mg/m^2/day may increase up to 200 mg/m^2/day
Verapamil		0.05–0.30 mg/kg over 3–5 minutes, maximum 10 mg, not under 12 months of age

should be considered while caring for patients with rhythm disturbances or those receiving chronic anti-arrhythmic therapy as necessary.

Class I agents

The largest group of anti-arrhythmic drugs are sodium-channel blockers. The relatively large size of this class of agents has led to its subclassification into IA, IB, and IC groups on the basis of each drug's cellular actions. Group IC consists of oral drugs only and is not discussed in this chapter.

Class IA agents

The class IA drugs include procainamide, quinidine, and disopyramide. Their predominant electrophysiologic effect is the prolongation of both myocardial repolarization (QT interval) and the action potential. The mechanism of action is primarily related to the inhibition of the fast sodium channels. The anticholinergic (vagolytic) properties of these drugs account for their more pronounced effects at fast heart rates.

Procainamide

Procainamide is a potent sodium-channel blocker and, to a lesser extent, a potassium-channel blocker. This drug slows atrial conduction (prolongs the PR interval) and lengthens the QRS duration and QT interval. Procainamide is useful in the management of both atrial and ventricular arrhythmias [26, 38, 88, 89]. The suppression of abnormal automaticity accounts for its usefulness in the treatment of EAT, JET, and VT. The drug is generally more effective than lidocaine in acutely terminating sustained VT.

Procainamide can be administered via the oral, IV, or intramuscular routes. For the treatment of acute arrhythmias, IV loading (doses of 10–15 mg/kg) over a period of 30–45 minutes is usually required. The lower end of the loading dose spectrum is suggested for younger patients. Continuous ECG monitoring and frequent blood pressure assessments are recommended during the loading phase. This drug is rapidly distributed after IV injection. After the

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loading dose is administered, an infusion is frequently initiated at the rate of 30–50 μg/kg/min. Monitoring plasma levels is advisable, and the maintenance infusion rate should be adjusted as needed to achieve therapeutic levels between 4 and 8 μg/mL. The drug is eliminated by the kidneys (50–60%) and through hepatic metabolism (10–30%). Hepatic acetylation generates N-acetylprocainamide (NAPA), a metabolite with anti-arrhythmic (class III) properties.

Potential side-effects of procainamide include hypotension due to blocking of alpha-adrenergic receptors and decreased systemic vascular resistance during rapid IV administration. Significant QT prolongation and proarrhythmia are also well described. Additional non-therapeutic effects include negative inotropy and AV block. Gastrointestinal symptoms, a lupus-like syndrome, and blood dyscrasias can also occur.

Class IB agents

Class IB drugs include lidocaine, mexiletine, phenytoin, and tocainide. These drugs inhibit fast sodium channels and shorten both the action potential duration and the refractory period.

Lidocaine

Lidocaine is a short-acting agent with primary effects on the ventricular myocardium. It is one of the anti-arrhythmic drugs that are more commonly used in operating rooms and intensive care units. It is effective for suppressing frequent ventricular ectopy and warning arrhythmias and for preventing the recurrence of VT and VF [90–93].

An initial IV bolus of 1 mg/kg is recommended that can be repeated after several minutes if ineffective. The maintenance infusion rate ranges between 20 and 50 μg/kg/min. Lidocaine is rapidly metabolized in the liver by microsomal enzymes. Therefore, drugs associated with altered microsomal enzyme activity and conditions that can potentially reduce hepatic blood flow (e.g., severe congestive heart failure) may impair drug metabolism. Monitoring drug levels is advisable during continuous infusion.

Lidocaine toxicity from excessive plasma concentrations can result from poor cardiac output or from hepatic or renal failure. Elevated plasma levels beyond the therapeutic range can cause gastrointestinal symptoms (nausea and vomiting), central nervous system pathology (paresthesias, tremor, confusion, seizures), and, in rare instances, hemodynamic perturbations.

Class II agents

The class II drugs (esmolol, atenolol, metoprolol, and propranolol) block ß-adrenergic receptors to variable extents (receptor selectivity and intrinsic sympathomimetic activity) depending on the specific agent. Anti-arrhythmic effects result from slowing conduction and decreasing automaticity, particularly in the sinoatrial and AV nodes. These drugs universally decrease sympathetic activity through the ß-receptor blockade.

Esmolol

Esmolol is a predominant $ß_1$-selective (cardioselective) adrenergic receptor-blocking agent with a rapid onset and a very short duration of action. The drug's primary electrophysiologic effect is inhibiting sinoatrial and AV conduction. Esmolol's brief elimination half-life after IV injection (approximately 9 minutes) has made this drug desirable for use in perioperative and intensive care settings. Esmolol is commonly used to control heart rate and blood pressure and to manage a variety of tachyarrhythmias (supraventricular and ventricular) [94, 95].

An IV loading dose of 100–500 μg/kg (over 1–2 minutes) can be administered. This is followed by a continuous infusion, starting at 50–100 μg/kg/min and titrated to effect. Because of esmolol's short half-life, blood levels of the drug can be rapidly altered by increasing or decreasing the infusion rate, and the drug can be rapidly eliminated by discontinuing the infusion.

Most of the reported adverse effects related to esmolol therapy have been mild and transient. Reported cardiovascular side effects include bradycardia, sinus pauses, AV block, hypotension, and negative inotropy. These are most likely to be seen during bolus therapy.

Class III agents

The class III drugs (amiodarone, sotalol, bretylium, ibutilide) block potassium channels and increase action potential duration and refractoriness in atrial and ventricular muscle and in Purkinje fibers. These agents should be avoided in patients with LQTS.

Amiodarone

Amiodarone has a wide spectrum of actions with multiple and complex electrophysiologic effects that encompass all four anti-arrhythmic drug classes. Class I drug actions include inhibition of fast sodium channels. Class II and IV effects result in depression of sinus node automaticity and function and slowing of AV and His–Purkinje system conduction. As a class III agent, amiodarone delays repolarization and increases action potential duration, thereby prolonging refractoriness in all cardiac tissues and accessory connections if present. In addition to blocking potassium channels, amiodarone has vagolytic properties, weakly blocks calcium channels, and noncompetitively blocks α- and ß-adrenergic receptors. The efficacy of this agent has been documented against many supraventricular (EAT, atrial flutter and fibrillation, reentrant arrhythmias involving accessory pathways, JET), and ventricular arrhythmias (VT and VF) [37, 96–98]. The usefulness of this drug in the treatment of life-threatening tachyarrhythmias accounts for its expanding role in emergency cardiovascular management. In patients with an ICD, amiodarone may affect defibrillation thresholds.

Intravenous therapy requires a loading dose because of amiodarone's rapid plasma disappearance during the distribution phase. The suggested dose in children is 5 mg/kg over 1 hour (may be given rapidly for life-threatening arrhythmias; max. dose 300 mg). The same dose is then infused over 12 hours and repeated if necessary. Amiodarone binds extensively to most tissues, which explains its extremely prolonged elimination and thus its unusually long half-life (average 58 days).

Amiodarone administration can result in sinus bradycardia and AV block. Hypotension and cardiovascular collapse

is another potential complication of IV therapy and is probably due to calcium chelation [99]. Electrocardiographic effects include PR, QRS, and QTc prolongation. There are significant drug interactions while using amiodarone that merit discussion. Co-administration with other anti-arrhythmic agents (digoxin, procainamide, flecainide, quinidine, phenytoin) can result in increased levels of these drugs. The concomitant use of the drug with ß-blockers or calcium-channel antagonists should raise concerns about potential synergistic effects on conduction tissue. Several adverse effects have been reported with long-term oral therapy in children. These include skin discoloration, corneal microdeposits, alterations in hepatic and thyroid function, pulmonary fibrosis, and neurologic disturbances.

Sotalol

Sotalol is another class III anti-arrhythmic that also has some weak beta-blocker effects. Its main anti-arrhythmic effect is by prolonging repolarization, thereby prolonging refractoriness in cardiac tissue. Intravenous sotalol has shown promise in the acute termination of supraventricular arrhythmias (EAT, atrial flutter, reentrant arrhythmias involving accessory pathways) and ventricular arrhythmias [39, 53–55, 100, 101]. When given for acute termination of arrhythmia the suggested dose for intravenous sotalol is 1 mg/kg over 1 hour or 30 mg/m^2 over 15 minutes. Sotalol has also been shown to be safe and effective in the chronic management of both supraventricular and ventricular arrhythmias [102]. Close monitoring of the QTc interval and telemetry is needed, particularly during initiation of therapy, as *torsades de pointes* is a potential adverse effect, particularly in patients with associated CHD. In rare cases, hypoglycemia has been reported in patients with poor oral intake [103].

Ibutilide

Ibutilide is a class III agent approved in the adult population for acute intravenous therapy of atrial flutter and fibrillation of recent onset (<90 days) [104–106]. Like other drugs that prolong ventricular repolarization, this agent can cause excessive QT prolongation and polymorphic VT, which necessitates careful patient selection and monitoring during drug administration. The clinical experience with ibutilide in pediatric patients is extremely limited [107, 108].

Class IV agents

The class IV drugs, also known as calcium-channel blockers (verapamil, diltiazem, nifedipine), inhibit the slow inward calcium current.

Verapamil

The actions of this drug are mediated through the prolongation of conduction time and refractory period in nodal tissue. Verapamil has been shown to be effective for managing SVT and certain types of VT [109–111].

Verapamil should not be used in young children (<1-year-old) because of its potential to cause severe hemodynamic compromise (refractory hypotension, myocardial depression, asystole and cardiovascular collapse) [112, 113]. The detrimental effects are related to calcium-channel blockade and uncoupling of excitation-contraction in myocardial cells. In older children (>1-year-old), verapamil is infused in a dose of 0.1 mg/kg. The concomitant use of verapamil and ß-blocking agents can result in serious cardiovascular side-effects and is therefore not recommended. In patients with WPW syndrome, verapamil can enhance the ventricular response rate of atrial fibrillation and lead to hemodynamic compromise.

Other agents

Atropine

Atropine sulfate, an antimuscarinic, parasympatholytic drug, accelerates sinus or atrial pacemakers and enhances AV conduction. Atropine is recommended for the treatment of symptomatic bradycardia caused by increased vagal activity or AV block, such as vagally mediated bradycardia during intubation. Atropine may be considered in the treatment of bradycardia associated with poor perfusion or hypotension; however, epinephrine is probably more effective for this condition. Efforts to ensure adequate oxygenation and ventilation and to exclude hypothermia should precede pharmacologic therapy of bradycardia.

The recommended dose is 0.02 mg/kg, with a minimum single dose of 0.1 mg and a maximum single dose of 0.5 mg in a child and 1.0 mg in an adolescent or young adult. The dose can be repeated 5 minutes later, to a maximum total dose of 1.0 mg in a child and 2.0 mg in an adolescent. In the absence of IV access, atropine (0.02 mg/kg) can be administered tracheally or intramuscularly, although with less reliable absorption than through the IV route. Small doses can be associated with transient heart rate slowing. Atropine can also rarely cause cardiac arrhythmias.

Digoxin

Digitalis glycosides have been used for many years in the management of certain arrhythmias. The electrophysiologic effects of digoxin are the result of its direct effects on cardiac tissues (through inhibition of the sarcolemmal sodium pump) and indirect effects via the autonomic (parasympathetic) nervous system. Digoxin increases the refractory period and decreases the conduction velocity of the specialized cardiac conduction system, slows the sinus rate (primarily by enhancing vagal discharge), and shortens the refractory period in atrial and ventricular muscle.

Digoxin can be effective in the treatment of a wide spectrum of supraventricular arrhythmias, such as SVT, atrial flutter, atrial fibrillation, and chaotic AT. In patients with WPW syndrome, digoxin is not recommended because it may alter the conduction properties of the accessory pathway and lead to malignant arrhythmias (VT and VF) during atrial flutter or fibrillation.

Digoxin can be administered orally or parenterally. Given that the onset of its effect may be delayed (up to 5 hours), this drug is less than ideal for treating acute symptomatic tachycardias. Despite this limitation, digitalis glycosides remain useful in controlling the ventricular response in atrial tachyarrhythmias, particularly during atrial flutter or fibrillation.

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A common loading algorithm uses a total oral digitalizing dose of 30–50 μg/kg. Half of this amount is given initially, followed by two doses at 6-hour intervals of 25% of the total dose. For IV use, the total digitalizing dose is reduced to 75% of the total oral dose given following a similar scheme. Maintenance doses of digoxin are 7–10 μg/kg/day. Digoxin binds tightly to peripheral tissue proteins, and drug excretion is via the kidneys. Dose adjustments are indicated in cases of renal impairment or congestive heart failure.

The co-administration of digoxin with other anti-arrhythmic agents (amiodarone, quinidine, verapamil) requires an adjustment (reduction) in the digoxin dose and monitoring of plasma levels. Toxic manifestations of digitalis therapy can be classified as cardiac and non-cardiac. Digoxin toxicity can cause virtually any type of cardiac rhythm disturbance. Non-cardiac manifestations of digitalis toxicity include gastrointestinal problems (nausea, vomiting, anorexia), neurologic symptoms (headache, lethargy, weakness, confusion, seizures), and visual disturbances. Although non-specific, non-cardiac symptoms are the earliest manifestations of digitalis toxicity.

Adenosine

Adenosine is a purine agonist, with effects mediated by the activation of the A_1 adenosine receptor, leading to activation of adenylate cyclase and intracellular cyclic adenosine monophosphate (cAMP) production. The electrophysiologic effects are secondary to an increase in potassium conductance and depression of the slow inward calcium current, resulting in transient sinus slowing or AV nodal block. This accounts for its therapeutic value in terminating arrhythmias that involve the AV node. Adenosine is the drug of choice for acute treatment of SVT [59, 60, 62, 114–116]. Adenosine can also aid the diagnosis of atrial tachyarrhythmias and may be useful in the differentiation of wide QRS tachycardias [116].

To terminate SVT, a bolus of IV adenosine is rapidly injected, preferably into a central vein, at initial doses of 100–150 μg/kg, followed by a rapid normal saline flush. The dose can be doubled up to a maximum of 300 μg/kg (or an adult dose of 6–12 mg). The effects of the drug are seen within 10–20 seconds. It is extremely useful to obtain an ECG recording during its administration because the response to adenosine may provide an insight into the mechanism of tachycardia. Adenosine is rapidly metabolized by erythrocytes and endothelial cells, accounting for its extremely short half-life (<10 seconds).

Cardiac side-effects include sinus pauses, sinus bradycardia, AV block, atrial and ventricular arrhythmias, and reflex sinus tachycardia. These effects are generally transient and may only necessitate supportive care. However, the availability of temporary pacing and an external defibrillator may be prudent. Adenosine should be used with caution in patients who have undergone cardiac transplantation because the electrophysiologic effects of this agent are increased in the denervated heart. Other unwanted effects are transient and generally well tolerated. These include flushing, shortness of breath, bronchospasm, and chest pressure. On very rare occasions, hypotension may occur.

Ivabradine

Ivabradine is a novel anti-arrhythmic drug that works by selectively inhibiting the pacemaker or "funny" current (I_f) in both the sinus and AV node. The I_f current is generated by a nonselective, hyperpolarization-activated cyclic nucleotide-gated transmembrane channel that allows for sodium influx into the cell and potassium efflux from the cell. By inhibiting this channel, ivabradine causes a decrease in the slope of diastolic depolarization and thus causes a reduction in heart rate. One of its benefits is that it causes a reduction in heart rate without affecting cardiac inotropy or systemic vascular resistance [41]. Its use was initially in adult patients with heart failure but applications in pediatric automatic arrhythmias are growing. Small case series and case reports have demonstrated good early results in the management of junctional and atrial ectopic tachycardias. For postoperative junctional tachycardias in pediatric patients, ivabradine has been used alone or in combination with amiodarone with promising results [40, 42, 43]. At this time the drug is only FDA approved for oral use and therefore limited to patients in which the oral route is available. Ivabradine's cardiac side effects include bradycardia, and atrial fibrillation, and its most common non-cardiac effect is visual disturbances. Ivabradine is metabolized by CYP3A4 so its use should be avoided in conjunction with CYP3A4 inhibitors as they can increase toxicity [41].

Magnesium sulfate

Magnesium is a major intracellular cation, a co-factor in multiple enzymatic reactions, and an important regulator of numerous cardiovascular processes. Magnesium sulfate therapy is indicated as adjunct management for arrhythmias in patients with documented hypomagnesemia or *torsades de pointes* [117]. Magnesium deficiency is frequently seen in patients with other electrolyte abnormalities (hypokalemia and hypocalcemia). Rhythm disturbances associated with hypomagnesemia resemble those with hypokalemia or digitalis toxicity.

In *torsades de pointes*, IV infusion (over several minutes) of 25–50 mg/kg (up to 2 g) is recommended. Approximately 70% of plasma Mg^{2+} is ultrafiltered by the kidney, and the remainder is bound to protein. Side-effects associated with drug administration include flushing, diaphoresis, muscle weakness, and central nervous system depression. Magnesium levels well above the therapeutic range can lead to serious morbidities, such as cardiac conduction defects, respiratory depression, and circulatory collapse.

Dexmedetomidine

Dexmedetomidine is an α_2-adrenoceptor agonist with primarily sedative properties recently shown to have anti-arrhythmic effects as well. The exact mechanism of these effects is not well understood. It appears that central α_2- adrenoceptor-mediated enhancement of vagal neural activity plays a potential role [118]. A prospective observational study showed that during the perioperative period after cardiac surgery, receiving a continuous infusion of dexmedetomidine lowered patients' risk of ventricular and supraventricular arrhythmias [30]. Other studies have also shown that the drug has a high success rate in the conversion of SVT [119, 120].

KEY POINTS: PHARMACOLOGIC THERAPY OF CARDIAC ARRHYTHMIAS

- Anti-arrhythmic agents suppress abnormal rhythms or restore normal rhythm and conduction by their effects on blocking sodium, potassium, or calcium channels, or by altering the adrenergic tone.
- Agents are usually categorized based on their mechanism of action into five main classes (Vaughan Williams classification).
- Some drugs have multiple sites of action, complicating the classification of these pharmacologic agents.
- Class III drugs should be avoided in patients with LQTS.
- The co-administration of certain anti-arrhythmic agents can result in increased levels of these drugs and potential synergistic effects on conduction.

Pacemaker therapy in children

Pacemaker nomenclature

Pacemaker nomenclature as established by the North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group is detailed in Table 22.6 [121]. The generic pacemaker (NBG) code has five positions. The first position or letter of the code refers to the chamber(s) paced, the second to the chamber(s) sensed, the third to the pacemaker's response to sensing, and the fourth to programmability and rate modulation. The fifth position is restricted to anti-tachycardia function and is used infrequently.

Permanent cardiac pacing

Advances in pacemaker technology, including enhancements in programmability and miniaturization of units, have resulted in the increasing use of these devices in infants and children [122]. Guidelines for device-based therapy of cardiac rhythm abnormalities have been published by various organizations and modified over the years [123–126]. Box 22.2 lists indications for children, adolescents, and patients with CHD for which there is general agreement that a pacemaker should be implanted (class I) and for which these devices are used frequently but diverging opinions exist regarding benefits (class II). The recommendations for bradycardia management for adult CHD were subsequently revised as noted in Box 22.3.

Box 22.2: Recommendations for permanent pacing in children, adolescents, and patients with congenital heart disease

Class I (indicated; benefit >>>> risk)
- Advanced second- or third-degree AV blocks associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output
- Sinus node dysfunction with correlated symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate
- Postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery
- Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction
- Congenital third-degree AV block in an infant with a ventricular rate <55 bpm or with congenital heart disease and a ventricular rate <70 bpm

Class IIa (reasonable; benefit ≫ risk)
- Prevention of recurrent episodes of IART in patients with CHD and sinus bradycardia; sinus node dysfunction may be intrinsic or secondary to anti-arrhythmic therapy
- Congenital third-degree AV block beyond the first year of life with an average heart rate <50 bpm, abrupt pauses in the ventricular rate that are two or three times the basic cycle length, or associated with symptoms due to chronotropic incompetence
- Sinus bradycardia, complex CHD, and either a resting heart rate <40 bpm or pauses in ventricular rate >3 seconds
- CHD and hemodynamic impairment due to sinus bradycardia or loss of AV synchrony
- Syncope that remains unexplained after careful evaluation of possible causes in a patient with prior CHD surgery complicated by transient complete heart block and residual fascicular block

Class IIb (may be considered; benefit ≥ risk)
- Transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block
- Congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, narrow QRS complex, and normal ventricular function
- Asymptomatic sinus bradycardia after biventricular repair of CHD with a resting heart rate <40 bpm or pauses in ventricular rate >3 seconds

AV, atrioventricular; CHD, congenital heart disease; IART, intra-atrial reentrant tachycardia.
Source: Epstein et al. [124]. Reproduced with permission of Elsevier.

In general terms, potential indications for pacemaker implantation can be listed as follows.
- Symptomatic sinus bradycardia
- Recurrent bradycardia-tachycardia syndromes
- Congenital complete AV block
- Advanced second- or third-degree AV block

An important consideration in patients with CHD is the correlation of symptoms with recommended criteria for

Table 22.6 Generic pacemaker code

Position I	Position II	Position III	Position IV	Position V
Chamber(s) paced	**Chamber(s) sensed**	**Response to sensing**	**Programmability, rate modulation**	**Anti-tachyarrhythmic function(s)**
O, none A, atrium V, ventricle D, dual (A +V)	O, none A, atrium V, ventricle D, dual (A +V)	O, none I, inhibited T, triggered D, dual (I + T)	O, none P, simple programmable M, multiprogrammable C, communicating R, rate modulation	O, none P, pacing S, shock D, dual (P + S)

Source: Bernstein et al. [121]. Reproduced with permission of John Wiley & Sons.

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Box 22.3:

Recommendations for Management of Bradycardia in Adults With Adult Congenital Heart Disease
Referenced studies that support recommendations are summarized in.

COR	LOE	RECOMMENDATIONS
I	B-NR	1. In adults with adult congenital heart disease (ACHD) and symptomatic SND or chronotropic incompetence, atrial based permanent pacing is recommended.
I	B-NR	2. In adults with ACHD and symptomatic bradycardia related to atrioventricular block, permanent pacing is recommended.
I	B-NR	3. In adults with congenital complete atrioventricular block with any symptomatic bradycardia, a wide QRS escape rhythm, mean daytime heart rate below 50 bpm, complex ventricular ectopy, or ventricular dysfunction, permanent pacing is recommended.
I	B-NR	4. In adults with ACHD and postoperative second-degree Mobitz type II atrioventricular block, high-grade atrioventricular block, or third-degree atrioventricular block that is not expected to resolve, permanent pacing is recommended.
IIa	B-NR	5. In asymptomatic adults with congenital complete atrioventricualar block, permanent pacing is reasonable.
IIa	B-NR	6. In adults with repaired ACHD who require permanent pacing for bradycardic indications, a bradycardia device with atrial antitachycardia pacing capabilities is reasonable.
IIa	C-EO	7. In adults with ACHD with preexisting sinus node and/or atrioventricular conduction disease who are undergoing cardiac surgery, intraoperative placement of epicardial permanent pacing leads is reasonable.
IIb	B-NR	8. In adults with ACHD with pacemakers. atrial-based permanent pacing for the prevention of atrial arrhythmias may be considered.
III: Harm	B-NR	9. In selected adults with ACHD and venous to systemic intracardiac shunts, placement of endocardial pacing leads is potentially harmful.

Abbreviations: *COR* class (strength) of recommendation); *LOE* (quality) of evidence; *B-NR* level b, nonrandomized; *C-EO* level c, consensus of expert opinion.
Source: Kusumoto et al. [126]. Reproduced with permission from Elsevier.

pacemaker placement in view of the physiologic alterations associated with structural heart disease or postoperative intervention(s). The use of these devices in young patients and those with CHD presents unique challenges and considerations, some of which are highlighted in the sections that follow [127, 128].

Implantation techniques

Permanent pacemaker implantation is performed via either the transvenous or the epicardial approach. These procedures usually take place under sterile conditions in the cardiac catheterization laboratory/electrophysiology suite, or in the operating room. In most infants and small children, the procedure requires a general anesthetic. In a select group of patients, mainly composed of older adolescents and adults, and depending on several factors, these types of procedures can be performed under local anesthesia with supplemental IV sedation.

The transvenous technique uses the subclavian vein as the most common site for access [129]. Under fluoroscopic guidance, pacing leads are advanced into the right atrium or ventricle, or both, and are fixed to the endocardium. After adequate lead sensing, capture thresholds, and impedances are documented, and the leads are attached to a generator, which is typically positioned in the pectoral region. The following are considered contraindications to transvenous pacing: intracardiac communication with the potential for right-to-left shunting, prosthetic tricuspid valve, unsuitable anatomy for transvenous access to cardiac chambers, and small patient size (<10 kg). Advantages of the transvenous route include greater generator longevity (because of lower pacing thresholds) and lower incidence of lead fractures, particularly in active children [130]. The disadvantages are potential narrowing or thrombosis of venous pathways, lead dislocation, risk of systemic embolization in patients with an intracardiac shunt, and possible endocarditis.

For epicardial implantation, the leads are attached to the epimyocardial surface of the heart. After appropriate testing, the leads are tunneled to the generator pocket [131]. This approach requires a subcostal, subxiphoid, thoracotomy, or sternotomy incision. Advantages of epicardial implantation include the ability for placement independent of cardiovascular pathology and avoidance of lead-related venous complications. Disadvantages include the invasiveness of the approach, higher incidence of lead failure, and early generator-battery depletion.

Leadless pacemakers have recently become available and have been used in adults with promising results [132].

The leadless pacemakers consist of a fully contained system that is placed via a transvenous approach in the right ventricle. Initial devices were limited to ventricular pacing, ventricular sensing and ventricular inhibition only (VVI setting), but newer devices have capabilities of ventricular pacing, dual chamber sensing and dual chamber inhibition (VDD) programming allowing for AV synchrony. Their use in the pediatric population is limited to small series. Although encouraging results have been demonstrated, several limitations exist for their widespread use in the pediatric population. These include the large size of the delivery sheath (27 French) and risk for vascular complications, and the limit of single-chamber pacing. Even with the new devices with VDD capabilities, the maximum track rate is 115 bpm which significantly limits its ability to provide AV synchrony in the pediatric population. Another concern is that although the leadless pacemakers are theoretically retrievable, long-term experience and data on retrievability are limited [133–135]. Thus, leadless pacemakers are mostly used for patients that require limited backup pacing.

Hardware selection and programming of devices

A variety of hardware options are available for cardiac pacing in infants and children. The selection of a particular generator system, a mode for pacing, and type of pacing leads is influenced by several factors, including patient size, indications for pacing, the requirement for specific programmability options, underlying cardiac pathology, and anticipated need for generator longevity.

Both single- and dual-chamber units are commercially available for permanent pacing in pediatric patients. Dual-chamber devices provide the benefit of AV synchrony, thereby allowing for the maintenance of the atrial contribution to ventricular filling, enhancing cardiac output, and lowering atrial pressures.

Cardiac resynchronization therapy (CRT) requires placing two separate pacing leads in the right and left ventricles (biventricular pacing). The leads are implanted using a transvenous (left ventricular pacing accomplished via lead in the coronary sinus) or epicardial approach. The goal is to allow for electrical and mechanical synchrony in patients with intraventricular conduction delays in order to improve hemodynamics. This type of therapy is being increasingly used in pediatric patients. The most common indication is ventricular dyssynchrony related to a variety of cardiac diagnoses [136–144]. A recent single-center study has shown that for pediatric patients with symptomatic heart failure and electrical dyssynchrony, the use of CRT therapy has led to improved heart transplant-free survival and decreased mortality compared to a control group [145].

Pacemaker malfunction

Pacemaker malfunction is most frequently caused by complications related to lead placement and integrity, failure to pace, failure to capture, under-or oversensing, phrenic nerve stimulation, and pacemaker-mediated tachycardia [146]. Pacemaker troubleshooting usually requires a 15-lead ECG, a rhythm strip, device interrogation to determine pacing and sensing thresholds, lead impedances, generator battery status and magnet rate, and a chest radiograph.

Children are considered to be at higher risk for lead failure and fracture than adults. These problems result in inappropriate pacemaker sensing or capture (underpacing or overpacing) and the potential need for pacemaker revision. Adjusting pacemaker settings can temporarily remedy these issues.

Perioperative considerations

Patients with cardiac rhythm devices require special perioperative considerations (Box 22.4). The preoperative assessment of the patient with a pacemaker should include a complete history, with emphasis on indications for initial implantation, pacemaker dependency and underlying rhythm, coexistent cardiovascular pathology (structural or acquired), the functional status of the patient, and symptomatology. In addition, a focused physical examination should be performed that includes planned or existent pocket generator location [147]. Preoperative testing should be undertaken as indicated, including a chest radiograph that shows the number, position, and integrity of the pacing leads. If pacemaker details are needed but are not available, the device may have a code that can be read on a chest radiograph and used to identify the unit's manufacturer/model.

Device interrogation should be part of a complete preoperative evaluation in all patients with implanted pacemakers who are scheduled for surgical intervention (cardiac or noncardiac) [147–150]. Consultation with a pediatric cardiologist/electrophysiologist to obtain details of unit type, settings, date of and indications for implantation, and underlying rhythm is highly recommended. The patient's pacemaker card, if available, may also provide relevant information.

Box 22.4: Perioperative management of patients with cardiac rhythm devices

Preoperative preparation
- Determination of the type of device and indication for pacing/ICD
- Assessment of underlying rhythm and pacemaker dependency
- Evaluation of device function (pacemaker check, ECG, CXR)
- Consideration of reprogramming to the asynchronous pacing mode
- Deactivation of rate-adaptive functions
- Disabling of anti-tachycardia function/defibrillation mode as appropriate

Intraoperative management
- Intraoperative monitoring (continuous ECG, monitoring of effective cardiac output; e.g., pulse oximetry, cuff blood pressure, arterial line)
- Availability of backup temporary pacing and cardioversion-defibrillation equipment
- Immediate availability of drugs (isoproterenol, emergency agents)
- Avoidance of electromagnetic interference (bipolar electrocautery preferable; place grounding pad so current passes far away from the pacemaker and leads)
- Availability of magnet (not to replace preoperative evaluation or to be used instead of reprogramming device)

Postoperative considerations
- Continuous ECG monitoring, pulse oximetry, cuff pressure, or arterial line
- Immediate availability at all times of backup pacing and cardioversion-defibrillation equipment
- Interrogation of the device, reprogramming as needed
- Reactivation of special modes (anti-tachycardia, defibrillation mode for ICDs, and others)

CXR chest radiograph, ECG electrocardiogram, ICD implantable cardioverter-defibrillator.

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Results of a recent 15-lead ECG should also be reviewed. Reprogramming may be necessary before the planned procedure to avoid potential problems with pacemaker malfunction related to electromagnetic interference (EMI), such as that produced by electrocautery or radiofrequency ablation. If there is a significant risk of EMI and the patient is pacemaker-dependent, it is recommended that the pacemaker be reprogrammed to asynchronous mode [116]. The introduction of bipolar leads, improved filters, and circuit shields has made modern devices less susceptible to EMI. The rate-responsive mode, if turned on, should be deactivated, as should anti-tachycardia modes. Several case reports suggest that incomplete perioperative evaluations can lead to adverse outcomes [151, 152]. Pacemaker dysfunction has been found in up to 12% of patients undergoing preoperative interrogation before undergoing non-cardiac surgery, highlighting the importance of preoperative assessment [153].

Regarding intraoperative management, it should be considered that unipolar electrocautery can interfere with pacemaker function, so bipolar electrocautery is preferred. The diathermy grounding pad should have good skin contact and be placed as far away from the device as possible. In addition to routine perioperative monitoring, which includes ECG and pulse oximetry, other modalities that confirm pulse generation during pacing, such as manual pulse palpation, auscultation (via precordial or esophageal stethoscope), and invasive arterial blood pressure monitoring, should be considered. Chronotropic agents and alternate pacing modalities (transcutaneous, transvenous, transesophageal, epicardial) should be readily available in the event of pacemaker malfunction and inadequate underlying heart rate. If defibrillation is required, the current should not be applied to or passed directly through the pulse generator, because this may damage the device circuitry.

A magnet should always be accessible to allow for transient asynchronous pacing if required. Most generators respond to magnet application by pacing asynchronously at a fixed rate (atrium paced, no atrial sensing or inhibition [AOO], ventricle paced, no ventricular sensing or inhibition [VOO], or dual chamber paced, no dual chamber sensing or inhibition [DOO]). It should be emphasized, however, that the settings of the asynchronous programmed stimuli for magnet mode vary among pacemaker units. Furthermore, at the generator end of life, the pacing rate on magnet application may differ (i.e., be slower) from the pre-specified magnet rate or cause pacing to stop altogether. In some cases, the application of a magnet over a programmable pacemaker during EMI (i.e., cautery) may result in generator reprogramming [154]. Therefore, a magnet should never be considered a substitute for preoperative pacemaker interrogation or programming, nor should it be used routinely over a pacemaker generator during surgery or to offset potential EMI. After the procedure is completed, the device should be retested and programmed to baseline settings as appropriate.

For further depth on this topic, the reader is referred to the updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Cardiac Implantable Electronic Devices published in 2020 [147].

Temporary cardiac pacing

The transvenous and epicardial routes are commonly used for temporary pacing, although the transthoracic (transcutaneous) and transesophageal approaches are also suitable in some cases. Indications for temporary cardiac pacing are not as clearly defined as those for permanent pacing [155]. The literature suggests that there is no need for the routine placement of temporary epicardial pacing wires after congenital heart surgery [156–158]. However, in patients who undergo surgical interventions such as the Fontan operation or procedures performed under circulatory arrest, or who have intraoperative arrhythmias, postoperative temporary pacing has been shown to improve hemodynamics; thus, such patients may benefit from the placement of epicardial pacing wires at the time of surgery [159].

Temporary pacing is achieved by placing special wires in the atrial and/or ventricular epimyocardium toward the completion of the surgical procedure and before sternal closure [6, 155, 160]. As previously stated, atrial wires usually exit to the right of the sternum and ventricular wires to the left. Wires should be clearly labeled to prevent confusion if there is no institutional convention. Pacing in the atrium and ventricle is termed AV sequential pacing. During pacing, the electrical impulse originates at the pulse generator – in this case, a temporary pacing box – and then flows through the wires. Unipolar and bipolar epicardial pacing leads are available. A unipolar lead is a single wire conductor (electrode at the tip), whereas a bipolar lead has two conductors within a single wire. During unipolar pacing, the electrical current flows from the electrode in contact with the heart (cathode, negatively charged) to a wire placed in the subcutaneous tissue that serves as the electrode (anode, positively charged) receiving the electrical impulse after the cardiac tissue is depolarized. In bipolar pacing, the electrical current flows through the electrode at the distal tip of the lead wire (negative cathode), and after stimulation of the heart, the signal returns to the more proximal electrode (positive anode). Bipolar systems tend to require less energy for pacing, and there is less electrical interference during sensing. The negative cathode (the epicardial wire in unipolar systems; the distal epicardial wire in bipolar units) should be clearly labeled; this is the wire that should be connected to the negative terminal of the pulse generator.

Several programmable settings are available in the external temporary pulse generator (single- or dual-chamber device). Depending on the unit, these include pacing rate, atrial or ventricular output amplitude (milliamperes, mA), atrial or ventricular sensitivity (mV) or asynchronous mode, A-V interval (milliseconds), post-ventricular atrial refractory period, and upper rate tracking. The most important parameters to be adjusted are rate, chamber output, and pacing mode. Adjustments in optimal sensing and pacing parameters are guided by the testing of thresholds. The following is a brief overview of pacemaker settings and how these parameters are adjusted:

- *Rate*. This should be set at a physiological rate for age, or to provide adequate cardiac output during the postoperative state. If overdrive suppression of an arrhythmia is needed, the rate is usually set 10–20% higher than the arrhythmia rate.
- *Sensitivity*. The sensing threshold represents the *minimum electrical activity that the pacemaker is able to sense*. The lower the sensitivity setting, the less electrical activity is required by the pacemaker to sense, or greater sensitivity. To determine sensitivity, the pacemaker rate is set lower than the

underlying rate in a synchronous pacing mode (AAI, VVI or DDD). The sensitivity number is then increased (lowering sensitivity) until the sense indicator on the generator stops flashing (this implies that the mode is being changed to asynchronous pacing; see below). The sensitivity setting (number) on the generator is then decreased (increasing sensitivity) until the sense indicator flashes with each cardiac depolarization. This setting represents the sensing threshold. Sensitivity is then set at half of the sensing threshold. Typically, if no underlying rhythm is present, sensitivity is set at 2 mV. It should be emphasized that setting the sensitivity to a higher number renders the pacemaker insensitive, meaning that the mode is changed from demand to asynchronous or fixed-rate pacing. Conversely, using a very low sensitivity setting could make the pacemaker oversensitive, potentially risking pacemaker inhibition (failure to pace) by inappropriate sensing of events that are interpreted as electrical cardiac activity.

- *Capture thresholds*. This parameter indicates the minimum amount of energy (current intensity) required to stimulate the action potential in the myocardium. To determine this setting, the pacemaker rate should be set above the underlying rate so that the pacemaker is consistently pacing the chamber being tested. The output is then slowly decreased until there is no longer capture of this chamber. *The minimum output at which capture is still present is the capture threshold*. *The output should be set at twice the capture threshold to increase the margin of safety*. Setting the output too high results in a higher incidence of inflammation and fibrosis at the lead connection and higher capture thresholds. Care should be taken during capture threshold testing in patients with no underlying rhythm.
- *AV delay*. This represents the PR interval. In most cases, this parameter is set automatically according to rate or to between 100 and 150 ms.

Temporary pacing may be necessary for maintaining adequate cardiac output in patients with bradyarrhythmias, abnormal AV conduction, AV asynchrony, and inadequate heart rates for the physiologic state [161]. It may also be helpful in individuals at risk of high-degree AV block and can be used to suppress, overdrive, or terminate tachyarrhythmias. As previously discussed, atrial recordings obtained through temporary pacing wires can also provide diagnostic information in certain types of rhythm disorders. In the care of patients who depend on temporary pacing for maintenance of adequate hemodynamics, it is extremely important to be attentive to pacemaker settings and capture thresholds, which should be interrogated on a daily basis [160]. Testing should include determining underlying rhythm, whether ongoing pacing is needed, and the battery status of the temporary pacemaker. It is preferred to lower the pacing rate until the endogenous rhythm comes through to determine the underlying rhythm, rather than decreasing the output until capture is lost, pausing or turning off the pacemaker, or detaching the leads. Alternate means of pacing should be available in the event of lead or pacemaker failure or malfunction. A second pulse generator and the battery should be available at all times. Temporary pacing can be discontinued when the indication for pacing resolves or when the transition to a permanent pacing system is required.

External cardiac (transcutaneous) pacing

In the mid-1980s, a transcutaneous external cardiac pacing system was patented and introduced by Dr. Paul Zoll [162]. Over the ensuing years, there was renewed interest in the field and further enhancements in the technology. Most devices currently available for transcutaneous pacing combine defibrillation/cardioversion capabilities and external pacing features. In children, emergency transthoracic pacing can be considered as a temporizing measure for symptomatic bradycardia (secondary to abnormal sinus node function or to complete AV block) [163]. Because transcutaneous pacing results in simultaneous atrial and ventricular activation, it should be recognized that optimal hemodynamics may not be achievable. This pacing modality has not been found to be effective in the treatment of asystole in children.

Transcutaneous pacing electrodes (pads) are selected according to patient size (smaller ones for children <15 kg). When gel pads are applied prophylactically, an ECG tracing obtained directly from the pads confirms adequate skin contact and proper cable attachment to the unit in case pacing is required. Device settings for pacing typically include heart rate and current output (mA). Most available models provide the option for demand or fixed pacing mode. After the desired heart rate and pacing modality are selected, the output is increased until capture is achieved. In emergency situations, pacing should be initiated at or near the maximum current output, and once the capture is documented, pacing can be gradually decreased to 5–10 mA above the capture threshold. Sedation may be necessary to improve pacing tolerance in the awake patient because this mode of pacing can be associated with discomfort (burning skin sensation, contraction of skeletal muscles). Prolonged periods of transcutaneous pacing can result in serious burns or skin trauma in infants and young children. In addition to monitoring for pacemaker capture by an ECG, ongoing clinical assessment of pulse, blood pressure, and adequacy of cardiac output should be undertaken.

Transesophageal overdrive pacing

An esophageal catheter can be used for atrial sensing, which provides diagnostic information and enables discrimination between supraventricular tachyarrhythmias. Using the esophageal route also allows for overdrive pacing of a variety of supraventricular rhythm disorders (e.g., atrial flutter, SVT). For this purpose, an electrode catheter is inserted into the esophagus and advanced to a location that corresponds roughly to the region behind the atrial mass, and an AEG is obtained to better position the catheter. Local anesthesia of the nasopharynx or oropharynx and/or sedation is generally necessary for introducing the catheter and preventing discomfort during atrial pacing. Standard cardiorespiratory monitoring should be performed throughout the procedure, and airway support should be provided as necessary. Emergency drugs and cardioversion/defibrillation equipment should be made readily available.

Implantable cardioverter-defibrillators

The primary purpose of an ICD is to prevent sudden death in patients at high risk. Although sudden cardiac death is

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uncommon in pediatric patients, those with certain conditions are at sufficiently high risk to make them suitable candidates for ICD implantation. These conditions include hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, LQTS, BrS, and a history of near sudden death events [164, 165]. Placement of an ICD may also be warranted in pediatric patients with operated CHD or a history of malignant arrhythmias.

Device implantation involves lead and generator placement. An issue of concern is the high rate of lead failure, which is reportedly 21% in children and young adults [166]. A subcutaneous ICD that does not require transvenous lead placement is also available but does not provide any pacing capabilities except for temporary post-shock pacing [167, 168]. At present, experience in the pediatric age group with ICD devices, in general, is limited but growing, and is reported mostly in a retrospective fashion [168–174]. Prospective trials are required to establish guidelines for use, address safety concerns, and evaluate long-term issues specific to children.

Anesthetic considerations in patients with ICDs relate primarily to potential surgical EMI (from electrocautery) and the need for an available external cardioverting/defibrillating device. Perioperative consultation with a specialist is therefore essential. In most cases, the device must be deactivated or adjusted before surgery. The application of a magnet temporarily deactivates most, not all devices; thus, it is not a substitute for reprogramming and should only be considered in emergencies. Careful evaluation and device programming are advisable at the conclusion of the surgical intervention to ensure patient safety.

KEY POINTS: PACEMAKER THERAPY IN CHILDREN

- Indications for permanent pacing in children in most cases relate to symptomatic sinus bradycardia, recurrent bradycardia-tachycardia syndromes, congenital complete AV block, and advanced second- or third-degree AV block.
- Patients with implanted cardiac rhythm devices require special perioperative considerations during anesthetic care.
- Temporary pacing wires are placed toward the end of surgery in patients who may require or potentially benefit from pacing perioperatively; the wires also serve to assist in arrhythmia recognition/treatment.
- The most important settings for temporary cardiac pacing are heart rate, chamber output, and pacing mode.
- Temporary pacemaker settings and thresholds should be interrogated on a daily basis in the postoperative period.
- A magnet should never be used as a replacement for preoperative pacemaker interrogation or reprogramming, nor should it be used intraoperatively to offset potential EMI.

Summary

A significant portion of cardiac anesthesia practice involves caring for patients affected by cardiac rhythm disturbances or who may develop perioperative or periprocedural arrhythmias. It is well recognized that patients with CHD, both children and adults, represent a subgroup who are particularly vulnerable to the negative hemodynamic consequences associated with alterations of cardiac rhythm. Adequate knowledge of cardiovascular diseases affecting cardiac rhythm, arrhythmia mechanisms, diagnosis, drug therapy, and alternative therapeutic options is essential for optimal patient care and limiting related morbidity.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

6 Batra AS, Balaji S. Post operative temporary epicardial pacing: When, how and why? Ann Pediatr Cardiol 2008;1:120–5. The review describes indications for temporary pacing, as well as technical considerations, complications, and current practice related to this mode of pacing.

21 Saul JP, Scott WA, Brown S, et al. Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, anti-arrhythmic drug trial. Circulation 2005;112:3470–7. Report of a double-blind, randomized, multicenter, dose–response study of the safety and efficacy of intravenous amiodarone in 61 children. The efficacy of the drug was found to be dose-related; adverse events were common and were also found to be dose-related.

27 Batra AS, Chun DS, Johnson TR, et al. A prospective analysis of the incidence and risk factors associated with junctional ectopic tachycardia following surgery for congenital heart disease. Pediatr Cardiol 2006;27:51–5. Prospective study designed to evaluate the incidence of, and risk factors for, postoperative junctional ectopic tachycardia after surgery for congenital heart disease.

65 Bar-Cohen Y, Silka MJ. Management of postoperative arrhythmias in pediatric patients. Curr Treat Options Cardiovasc Med 2012;14:443–54. A review addressing the management of postoperative arrhythmias after pediatric cardiac surgery.

67 O'Hare M, Maldonado Y, Munro J, et al. Perioperative management of patients with congenital or acquired disorders of the QT interval. Br J Anaesth 2018;120:629–44. A review addressing important aspects of the congenital long QT syndrome, including definition, congenital LQTS versus acquired QT prolongation, clinical features, treatment, and anesthesia implications. Suggestions are given for anesthetic management.

126 Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2019;140:e382–482. Most recent guidelines addressing, among other subjects, recommendations for management of bradycardia in adults with CHD.

147 American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Cardiac Rhythm Management Devices. Practice advisory for the perioperative management of patients with cardiac implantable electronic devices: Pacemakers and implantable cardioverter-defibrillators 2020: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Cardiac Implantable Electronic Devices. Anesthesiology 2020;132:225–52. A comprehensive statement by the American Society of Anesthesiologists regarding the perioperative management of patients with cardiac rhythm devices. The guidelines are intended to facilitate safe and effective perioperative care of patients with these devices and to reduce the incidence of adverse patient outcomes.

CHAPTER 23
Airway and Ventilatory Management

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Introduction

Airway and ventilatory management of infants and children with congenital heart disease (CHD) during diagnostic and therapeutic procedures presents unique challenges to the anesthesiologist. This is a consequence of the interplay of a range of congenital airway abnormalities, cardiopulmonary interactions, and adverse effects of surgery and cardiopulmonary bypass on the respiratory system. Few other clinical situations will tax the skills of an anesthesiologist as the management of a child with CHD and a difficult airway. Children with cardiovascular disease may be intolerant of the myocardial depressant effects of many anesthetics, limiting the options available in managing their airway and circulation during induction of anesthesia. Children with cyanotic congenital heart disease experience rapid oxygen desaturation during periods of apnea associated with tracheal intubation. Moreover, in patients with single-ventricle disease, the very use of positive-pressure ventilation may limit pulmonary blood flow, leading to rapid decompensation. Developing a plan that allows safe airway and ventilatory management without hemodynamic compromise requires preparation, skill, and familiarity with a range of techniques of tracheal intubation and mechanical ventilation.

Choosing the appropriate endotracheal tube (ETT)

The narrowest portion of a child's larynx is at the level of the cricoid cartilage, as opposed to adult patients whose limiting airway diameter is at the level of the vocal cords (rima glottidis). Uncuffed ETTs have traditionally been used in young children because a seal may be created between the tracheal mucosa and the tube at the level of the cricoid cartilage so that a cuff may not be needed to create a seal [1]. A disadvantage of uncuffed ETTs is that the placement of an ETT with a gas leak at low inflating pressures (e.g., <15 cm H_2O) results in excessive leak around the endotracheal tube when lung compliance is poor. This is particularly important for thoracic or cardiovascular surgery because lung compliance may be reduced as a result of surgical traction, pulmonary edema, or atelectasis related to cardiopulmonary bypass (CPB). This results in a greater percentage of gas leak around the ETT. Gas leakage representing more than 50% of tidal volume has been demonstrated in the setting of decreasing lung compliance [2]. Associated decreases in minute ventilation may lead to hypoxemia due to atelectasis and intrapulmonary shunt as well as dangerous elevations in $PaCO_2$ related to decreased alveolar ventilation. Table 23.1 presents a scheme for selection of ETT size in infants and children.

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Table 23.1 Endotracheal tube sizes used in pediatric patients

Age	Size (mm ID)
Preterm	
<1000 gm	2.5
1000–2500 gm	3.0
Term Neonate – 6 months	3.5
6 months to 1 year	4.0
1–2 years	4.0–5.0
Beyond 2 years	$\frac{\text{Age (years)}}{4} + 4$

In addition to the risk of inadequate alveolar ventilation, there are other hazards associated with placement of a loose fitting ETT. Lung function measurements are commonly used to guide mechanical ventilation in the postoperative period. A variable leak around the ETT results in inaccurate measurements of exhaled tidal volumes, lung compliance, and airway resistance. A significant gas leak around the ETT also results in environmental pollution from either inhaled anesthetic agents or nitric oxide [3]. Lastly, an inadequate seal around the ETT may increase the risk of pulmonary aspiration should gastric contents be regurgitated during positive pressure ventilation.

Traditional airway management has included the use of uncuffed ETTs in children under the age of 8 years. However, there is limited scientific evidence to support this practice. Since the mid-1990s, advancements in the materials used in the ETT cuff, the shape of the cuff itself, and the relative outer diameter of the inflated cuff have lowered the risk for airway injury with the use of cuffed ETT's [4–6]. Cuffed endotracheal tubes are now routinely placed in infants and children, and the incidence of clinically significant airway complications is very low [7]. The use of cuffed ETTs during anesthesia reduces the need for repeated laryngoscopy and tracheal intubation, allows use of lower fresh gas flows, and limits environmental contamination with anesthetic gases [2]. There is no difference in the incidence of airway complications in pediatric patients intubated with cuffed vs. uncuffed endotracheal tubes during anesthesia or in pediatric intensive care units [7, 8]. However, the need to exchange endotracheal tubes is significantly greater when using uncuffed ETTs. Decreased lung compliance from the effects of cardiopulmonary bypass may increase the leak around the endotracheal tube in children after heart surgery, and a cuffed ETT may be partially deflated to compensate for such changes. In a retrospective review of 809 children <2 years old undergoing cardiac surgery over a 4-year period, the incidence of subglottic stenosis (17/809 or 1.08%) was not affected by the use of uncuffed vs. cuffed ETTs. The most important risk factors for subglottic stenosis were younger age and prolonged (>96 hours) postoperative intubation [9]. There is some evidence suggesting that children with CHD require larger endotracheal ETTs regardless of the duration of surgery [10]. Given this information, the pediatric patient requiring lengthy surgical intervention for congenital heart disease and/or a significant period of post-operative mechanical ventilation will generally benefit from the use of a cuffed endotracheal tube.

A disadvantage of using cuffed ETTs is that their outer diameter is approximately 0.3–0.5 mm larger than uncuffed ETTs with the same inner diameter. As a result, a tube with an inner diameter one size (i.e., 0.5 mm ID) smaller is recommended when a cuffed ETT is placed. The reduction in ETT internal diameter results in greater resistance to gas flow and an increased risk of occlusion of the ETT with blood and tracheal secretions. While a reduction of the tracheal tube diameter by only 0.5 mm might not be expected to effect a clinical change, gas flow resistance increases exponentially at smaller tube diameters. While a reduction in tracheal tube size from 8.0 mm ID to 7.5 mm ID increases airway resistance by 29%, a change from a size 4.0 mm ID to a 3.5 mm ID tube results in an increase of 71%, and a change from a 3.5 mm ID tube to a 3.0 mm ID tube increases resistance by 85%. The increase in resistance is even more profound if turbulent airflow occurs in smaller tracheal tubes. In addition, use of ETTs with a smaller internal diameter may result in the need to use smaller suction catheters, limiting the ability to effectively clear blood and secretions from the airways.

The Microcuff® endotracheal tube (Kimberly Clark; Roswell, GA) has been developed for pediatric patients. This ETT includes a true high-volume / low-pressure cuff, eliminates the Murphy eye in order to optimize cuff position at the tip of the endotracheal tube, and includes an ultrathin cuff that provides an outer diameter-to-inner diameter ratio similar to uncuffed endotracheal tubes. The Microcuff® ETT may decrease the incidence of micro-aspiration around the ETT cuff. While conventional PVC cuffs create folds and channels when inflated that allow fluid to leak past the cuff, the cuff on the Microcuff® ETT is designed to minimize those channel openings to create a more effective tracheal seal. The cuff length and shape of Microcuff® ETTs are also designed for better contact with tracheal contours to increase protection against fluid leakage. Of note, the lack of a Murphy eye eliminates a channel for gas exchange in the case of an ETT placed too distally in the trachea or in the right mainstem bronchus.

Two studies including 575 patients age 0–5 years have found a low incidence of post-extubation stridor, and a tracheal tube exchange rate of <3% when cuffed ETTs are used in children [11, 12]. A combined analysis of 3 controlled randomized trials of cuffed vs. uncuffed ETTs in 2804 children less than 8 years of age concluded that there was no difference the incidence of post-extubation stridor requiring treatment with racemic epinephrine or corticosteroids, or of the need for reintubation or need for ICU care [13]. In patients who underwent surgery for congenital heart disease and were managed with Microcuff® ETTs, a retrospective review of 208 patients weighing less than 5 kg found no cases of tracheal stenosis. However, 20.9% of patients developed stridor requiring treatment with racemic epinephrine and 2 patients had severe stridor requiring reintubation [14].

Orotracheal vs. nasotracheal intubation

While orotracheal intubation is performed more commonly than nasotracheal intubation for most surgery in children, many centers routinely place nasal ETTs in children undergoing cardiac surgery. Intraoperative transesophageal echocardiography (TEE) may cause dislodgement of an oral ETT, although

a low incidence of airway complications during pediatric TEE among children who were orally intubated has been reported [15]. Of the 1650 patients studied, 3 (0.2%) developed a right mainstem advancement of the ETT and 8 (0.5%) were inadvertently extubated. Nasal ETTs are more readily secured to the face, and movement of the ETT is less likely during manipulation of the TEE probe. While nasal intubation may minimize risk of pressure injury from the ETT to the lips, there is a greater risk of damage to nasal alae and, in older children, of sinusitis from long-term nasotracheal intubation [16–18]. These risks may increase if nasotracheal intubation is utilized infrequently and care providers in the post-operative phase (e.g., respiratory therapists, bedside nurses, etc.) are unaware of the need to monitor for such complications. Therefore, for patients whose operative course predicts a lengthy ICU stay, institutional familiarity with nasotracheal intubation should be considered in advance. The risk of bleeding from nasal mucosal or adenoidal trauma is especially problematic in the fully anticoagulated patient. This risk is minimized by the routine use of topical vasoconstrictor drugs (e.g., oxymetazoline), adequate lubrication, and warming of the ETT prior to placement. Excessive pressure should not be used during advancement of the tube through the nose and nasopharynx. Prior to advancing the ETT into the nasopharynx, a soft, lubricated, tapered suction catheter can be affixed to the tip of the ETT and advanced through the nasopharynx; it can be gently pulled through the mouth using a laryngoscope and Magill forceps, guiding the ETT into the oropharynx. The catheter acts as a guide permitting easier passage of the nasal ETT through the nasal passages and nasopharynx. The catheter is then removed from the ETT, allowing placement of the ETT into the trachea using the laryngoscope and Magill forceps [19].

Because ETTs can be placed more easily and rapidly via the oral route, oral intubation is preferred for rapid sequence intubation or during emergencies. Once adequate ventilation and oxygenation have been provided and the stomach is suctioned, the ETT may be exchanged for a nasal tube under direct visualization. In general, the nasal passages of children will accommodate the same size ETT as would be used for oral intubation.

An analysis of 26,754 cardiac surgery cases from the multicentered Congenital Cardiac Anesthesia Society database compared the outcome of patients who had oral vs. nasal endotracheal intubation [20]. Nasal intubation was performed in 41% of neonates, 38% of infants, 15% of school aged children, and 2% of adolescents; about 80% of neonates and infants had cuffed ETT. There were fewer accidental extubations in neonates who were nasally intubated (0% vs. 0.37%). However, after 12 months of age nasal intubation was associated with an increased risk of infection (mediastinitis, wound infection, pneumonia, septicemia). The duration of mechanical ventilation and hospital stay were not different between groups.

The difficult airway

The incidence of noncardiac congenital airway anomalies is believed to be greater among children with congenital heart disease than in the general population. Certain genetic disorders are clearly associated with both airway anomalies and congenital heart disease, including CHARGE and velocardiofacial (DiGeorge) syndrome (22q11 deletion). Children with these anomalies should have a complete airway examination, including endoscopic subglottic examination, by an otolaryngologist prior to cardiac surgery. In older, cooperative patients, the airway should be examined as with adult patients, including mouth opening, dentition, mandibular size, hyomental distance, and neck mobility. Studies in adults have shown that examination of the airway can help predict difficulty of intubation and mask ventilation [21]. No such studies have been performed in infants and children, and it is not known whether assessing mouth opening using a tongue depressor in a nonverbal child is predictive of difficulty with intubation. Assessment of an infant's airway should include an assessment of neck mobility and the appearance of the mandibular size when viewed in profile. Children with micro- or retrognathia are more likely to manifest difficult mask ventilation and/or difficult intubation.

The incidence of difficult intubation is higher among children with CHD. A study of 11,219 children from the population at large undergoing general anesthesia found 1.35% of patients had difficult intubation, defined as a Cormack-Lehane view of Grade 3 or higher [22]. The incidence for cardiac surgical patients was 3.6%, a higher incidence than any other group surgical group, including craniofacial surgery. Neonates and infants had a higher incidence of difficult intubation, 2.5% for the general population and 6.9%, for the cardiac surgical group. These same authors reported a detailed analysis of 1,177 pediatric cardiac surgery cases [23]. Interestingly, Trisomy 21 was not associated with difficult intubation; however, 9 of 29 patients (31%) with other genetic/dysmorphic syndromes were found to have difficult intubation (Table 23.2) [23]. They again found a higher incidence associated with younger age; difficult intubation was found in 5.6% of patients less than 12 months vs. 1.7% for older children.

A separate retrospective database review of 4,797 patients with CHD from a single center undergoing 8,657 anesthetics for cardiac and non-cardiac procedures found the incidence of difficult intubation to be about the same as that reported for the general pediatric population - 53 (1.1%) of the patients had a Cormack-Lehane grade 3 or higher [24]. In this report, 16.7% of patients had a genetic or dysmorphic syndrome, including Trisomy 21 (6%), velocardiofacial syndrome (3.6%), and CHARGE association (3%). Altogether 2.4% of patients required 3 or more intubation attempts. Video laryngoscopy was utilized in 7.7% of patients and fiberoptic bronchoscopy

Table 23.2 The number of patients with concomitant congenital syndromes and laryngoscopy grade [23]

Syndrome	CML I, II	CML III, IV
Microdeletion 22q11 / DiGeorge	6	4
VACTERL / CHARGE syndrome	5	3
Ullrich-Turner syndrome	5	0
Goldenhar syndrome	0	1
Pierre Robin sequence	0	1
Marfan syndrome	4	0

Abbreviation: CML, Cormack and Lehane classification

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in only 4 patients (0.1%). A significant percentage (18.2%) of patients had a congenital or acquired upper or lower airway anomaly (Tables 23.3 and 23.4).

During embryologic development, the tracheobronchial tree and the pulmonary vasculature develop together, and therefore, abnormalities of the pulmonary vasculature are often associated with abnormalities of the airway. This was confirmed in a review of 564 patients with tetralogy of Fallot/pulmonary atresia/major aortopulmonary collateral arteries (TOF/PA/MAPCAs) where 37% of the patients had velocardiofacial syndrome. Difficult intubation was noted in 5% of patients, and the incidence was not different among those with or without a chromosome anomaly [25]. Over 40% of the patients had perioperative bronchoscopy and/or chest CT scan and half of these patients had an upper or lower airway abnormality.

Table 23.3 Incidence of congenital and acquired airway abnormalities

Patients	***n* = 4797** ***n* (%)**
Airway abnormality	
Acquired airway abnormality	463 (9.7)
Vocal paralysis unilateral partial	179 (3.7)
Vocal paralysis unilateral total	137 (2.9)
Bronchomalacia	103 (2.1)
Subglottic stenosis	73 (1.5)
Vocal paralysis bilateral partial	15 (0.3)
Vocal paralysis bilateral total	2 (0.05)
Congenital airway abnormality	408 (8.5)
Laryngomalacia	227 (4.7)
Bronchomalacia	223 (4.6)
Laryngeal cleft	199 (4.1)
Subglottic stenosis	171 (3.6)
Tracheomalacia, tracheal stenosis, tracheal disease	134 (2.8)
Agenesis of lung	48 (1.0)

Source: Reproduced with permission from Foz et al. [24].

Table 23.4 Patient demographics and intubation details

Variable	**Median (IQR)** **or *n* (%)**
N (patients)	4,797
Age (y)	1.3 (0.2–6.0)
Weight (kg)	9.2 (4.3–19.2)
Sex	
Female	2,156 (45)
Male	2,638 (55)
Prematurity (≤36 weeks)	1,141 (23.8)
Airway (*n* = 8,657 patient-encounters)	
Airway in situ	1,724 (20.0)
Tracheostomy	29 (0.3)
Natural airway	46 (0.5)
Intubated at time of the procedure	6,858 (79.2)
Intubation attempts (*n* = 6,139 intubated patient-encounters)	
1	5,359 (87.3)
2	628 (10.2)
3	119 (1.9)
4	20 (0.3)
5+	13 (0.2)
Intubation technique	
Direct laryngoscopy	5,567 (92.3)
Video laryngoscopy	462 (7.7)
Flexible fiberoptic	4 (0.1)
Outcomes	
Difficult intubation	53/4,797 (1.1)

Abbreviations: IQR, interquartile range.

Source: Reproduced with permission from Foz et al. [24].

Efficient airway management with minimal periods of interrupted oxygenation and ventilation is of the utmost importance in infants and children with heart disease. Especially at risk are patients with cyanotic lesions, poor ventricular function (systolic and/or diastolic), and pulmonary hypertension. In children with cyanotic heart disease, the oxygen saturation of coronary blood is decreased. Additional oxygen desaturation during airway management may result in critically diminished oxygen delivery to cardiac myocytes. Coupled with the increase in plasma catecholamines associated with airway maneuvers, causing increased myocardial oxygen demand, significant myocardial ischemia may ensue. Children with low cardiac output have compromised coronary blood flow at baseline, and a decrease in oxygen saturation in coronary blood occurring while oxygen demand is increased during airway management may also result in severe myocardial hypoxia-ischemia. In children with pulmonary hypertension, a similar increase in plasma catecholamine concentrations coupled with any rise in $PaCO_2$ may cause an acute exacerbation in pulmonary vascular resistance and cardiac arrest. While anesthetic agents may prevent marked increases in sympathetic response to laryngoscopy and tracheal intubation, they may also cause myocardial depression and systemic hypotension, resulting in reduced coronary blood flow causing ischemia. Given these elevated risks for decompensation, and the relatively high frequency of airway anomalies, robust preoperative airway assessment and the preparation for a potential difficult intubation (e.g., ensuring availability of a video laryngoscope) is recommended.

Intubation of the patient with a difficult airway

A modification of the American Society of Anesthesiologists algorithm for the management of the patient with a difficult airway can be applied to children [26] (Figure 23.1). Specialized airway equipment should be prepared, checked and available in the operating room. Box 23.1 lists recommendations for equipping a difficult airway cart. In addition to equipment, additional personnel skilled in airway management should be immediately available for assistance.

When the difficult airway is recognized prior to the induction of anesthesia, control of the airway can be performed with the patient awake, following sedation, or after the induction of anesthesia with inhalation agents. Awake, nonsedated, direct laryngoscopy can be accomplished in neonates but may be difficult, traumatic, and have significant adverse hemodynamic consequences. Placement of a supraglottic airway (SGA) after application of topical anesthesia to the airway in an awake infant has been described as an

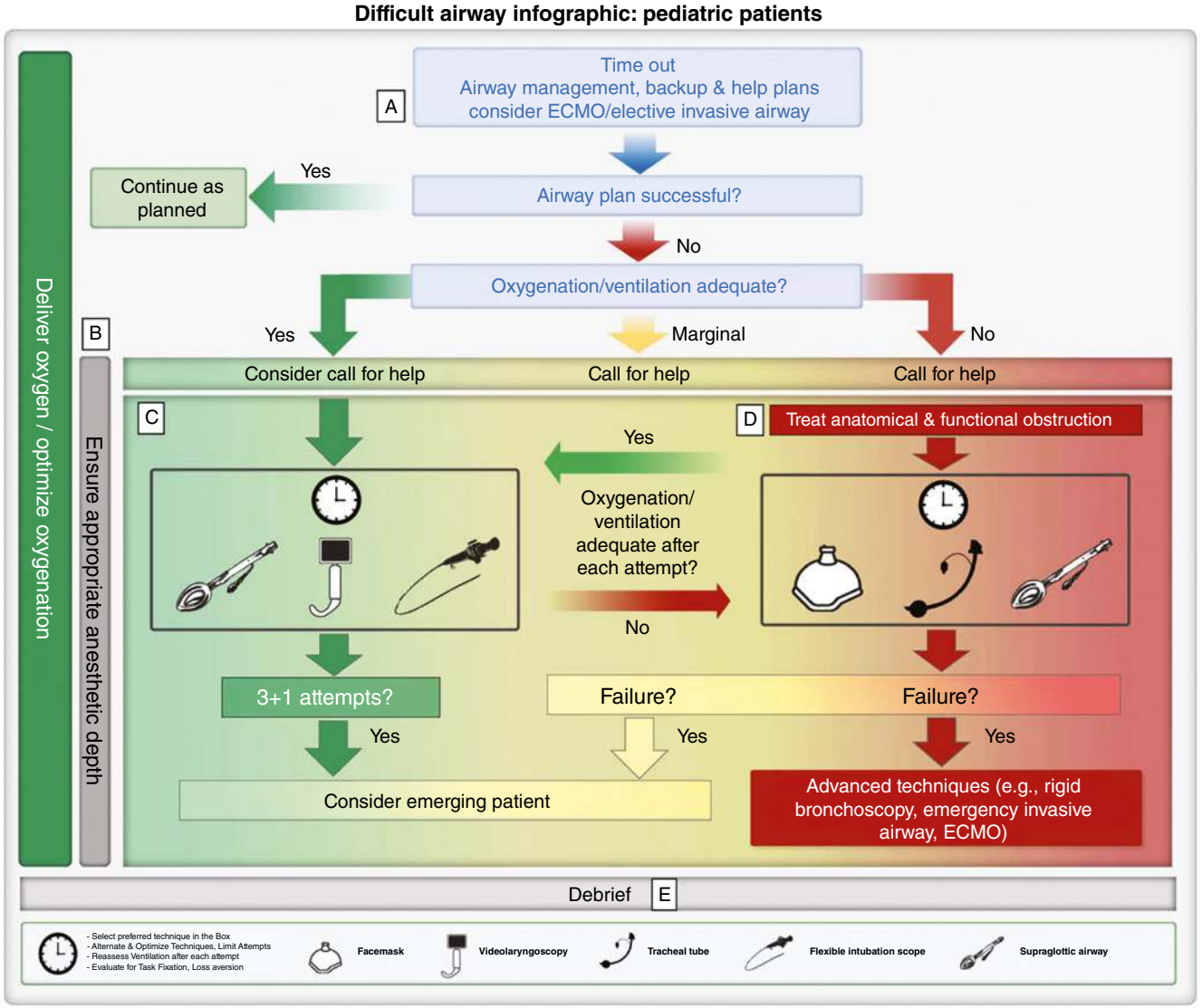


Figure 23.1 Difficult airway infographic: Pediatric patient example. (A) Time Out for identification of the airway management plan. A team-based approach with identification of the following is preferred: the primary airway manager and backup manager and role assignment, the primary equipment and the backup equipment, and the person(s) available to help. Contact an ECMO team/otolaryngologic surgeon if noninvasive airway management is likely to fail (e.g., congenital high airway obstruction, airway tumor, etc.). (B) Color scheme. The colors represent the ability to oxygenate/ventilate: green, easy oxygenation/ventilation; yellow, difficult or marginal oxygenation/ventilation; and red, impossible oxygenation/ventilation. Reassess oxygenation/ventilation after each attempt and move to the appropriate box based on the results of the oxygenation/ventilation check. (C) Nonemergency pathway (oxygenation/ventilation adequate for an intubation known or anticipated to be challenging): deliver oxygen throughout airway management; attempt airway management with the technique/device most familiar to the primary airway manager; select from the following devices: supraglottic airway, videolaryngoscopy, flexible bronchoscopy, or a combination of these devices (e.g., flexible bronchoscopic intubation through the supraglottic airway); other techniques (e.g., lighted stylets or rigid stylets may be used at the discretion of the clinician); optimize and alternate devices as needed; reassess ventilation after each attempt; limit direct laryngoscopy attempts (e.g., one attempt) with consideration of standard blade videolaryngoscopy in lieu of direct laryngoscopy; limit total attempts (insertion of the intubating device until its removal) by the primary airway manager (e.g., three attempts) and one additional attempt by the secondary airway manager; after four attempts, consider emerging the patient and reversing anesthetic drugs if feasible. Clinicians may make further attempts if the risks and benefits to the patient favor continued attempts. (D) Marginal/emergency pathway (poor or no oxygenation/ventilation for an intubation known or anticipated to be challenging): treat functional (e.g., airway reflexes with drugs) and anatomical (mechanical) obstruction; attempt to improve ventilation with facemask, tracheal intubation, and supraglottic airway as appropriate; and if all options fail, consider emerging the patient or using advanced invasive techniques. (E) Consider a team debrief after all difficult airway encounters: identify processes that worked well and opportunities for system improvement and provide emotional support to members of the team, particularly when there is patient morbidly or mortality. Developed in collaboration with the Society for Pediatric Anesthesia and the Pediatric Difficult Intubation Collaborative: John E. Fiadjoe, M.D., Thomas Engelhardt, M.D., Ph.D., F.R.C.A., Nicola Disma, M.D., Narasimhan Jagannathan, M.D., M.B.A., Britta S. von Ungern-Sternberg, M.D., Ph.D., D.E.A.A., F.A.N.Z.C.A., and Pete G. Kovatsis, M.D., F.A.A.P [26].

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Box 23.1: Suggested contents of difficult airway management cart

Rigid laryngoscope blades of alternate design and size from those routinely used.
Endotracheal tubes of assorted size. Nasal and oral airways of assorted sizes
Endotracheal tube guides and tube exchangers. Examples include (but are not limited to) semi-rigid stylets with or without a hollow core for jet ventilation and light wands.
Jet Ventilation Equipment
Fiberoptic intubation equipment.
Laryngeal mask airways of assorted size.
Equipment suitable for emergency surgical airway access (e.g., percutaneous cricothyrotomy).
Size 3.5, 4.0, 6.0
An exhaled CO_2 detector.

alternative to awake direct laryngoscopy [27]. Fiberoptic-guided intubation of the older, cooperative patient using topical anesthesia and intravenous sedation is a safe and effective alternative. Maintaining oxygenation via nasal cannula, nasopharyngeal airway with 15 mm connector, modified Ring-Adair-Elwyn ETT, or heated humidified high-flow nasal cannula should be considered during difficult airway management [28].

Inhalation induction of anesthesia using sevoflurane with maintenance of spontaneous ventilation is commonly performed in infants and children with a difficult airway. Intravenous access is established prior to mask induction. If the patient develops airway obstruction during the induction of anesthesia, immediate attempts are made to relieve the obstruction by head extension, jaw thrust, use of continuous positive airway pressure, and insertion of an oropharyngeal or nasopharyngeal airway. Oropharyngeal airway use may be of particular benefit in patients with glossomegaly such as those with Trisomy 21. If mask ventilation is inadequate and not improved with the above maneuvers, insertion of an SGA should be attempted. If positive pressure ventilation can be delivered via the SGA, the SGA can be used as a guide for insertion of an ETT or can be exchanged for an ETT with the use of a fiberoptic bronchoscope (FOB). If an SGA fails to provide a patent airway, preparations should be made for an emergency cricothyrotomy (see below). If mask ventilation is possible with either a face mask or SGA, neuromuscular relaxation can be used in order to optimize laryngoscopy. Recent data indicates that neuromuscular blockade can facilitate difficult mask ventilation and successful tracheal intubation. Moreover, with the ability of sugammadex at 16 mg/kg dose to reverse even profound neuromuscular blockade from non-depolarizing drugs, this approach can now be utilized with more confidence [3].

If mask ventilation is possible, but tracheal intubation is not readily achieved, one should optimize head and neck positioning and consider use of an alternate laryngoscope blade or video-laryngoscope to better visualize the larynx (the latter is often utilized as a primary device when difficult intubation is anticipated). Repeated attempts at direct laryngoscopy may lead to swelling and/or bleeding in the airway and the inability to perform adequate mask ventilation. After 3 failed attempts at direct laryngoscopy, the use of an SGA should be considered. For the majority of pediatric patients, insertion of an SGA provides a patent airway, a method of delivering positive pressure ventilation, and facilitates fiberoptic intubation.

For the patient with the known difficult airway requiring endotracheal intubation (e.g., those with predictably lengthy OR courses or predicted to require mechanical ventilation after surgery), visualization of the airway may be aided by video laryngoscopy. Devices such as the Glidescope

video laryngoscope (Verathon Medical, Bothwell, WA, USA) provide a highly angulated blade with a distal camera lens. The curve of this blade is designed to visualize structures "behind" the anatomic curve of the larynx, thereby aiding practitioners in obtaining a meaningful view of the vocal cords. The device is available in a wide range of pediatric sizes and some clinical studies demonstrating reduced time to intubation through its use [29]. However, the curve of this device requires a unique placement technique and not all practitioners may be familiar with its use. In addition, the disposable plastic blade cover is bulky and may interfere with passage of the ETT. The C-MAC (Karl Storz Endoscopy, Tuttlingen, Germany) couples standard Miller and Macintosh blades of multiple sizes with a distal fiberoptic lens. This allows for both direct laryngoscopy and/or video laryngoscopy using one device. Moreover, the angulation and distal position of the fiberoptic lens can provide an improved view of the difficult airway. Several studies have demonstrated improved pediatric intubation times with the use of this device [30].

Video laryngoscopy has become an essential tool in the management of the difficult intubation in patients of all ages, and a number of devices are available. Recent studies report the first attempt success rate is significantly higher with a video larygoscope than standard direct laryngoscopy in infants with normal airways [31]. In addition, a standard-blade video laryngoscope has a higher success rate on the first attempt (and eventual successful intubation) compared to a hyper-angulated blade video laryngoscope among infants less than 5 kg [32] (Figure 23.2).

Fiberoptic-guided tracheal intubation

The development of FOBs with small diameters has facilitated the use of fiberoptic-guided intubation in infants and young children. The FOBs designed for use with a 3.5 mm ID ETT or smaller do not have an associated suction channel. Fiberoptic guided tracheal intubation can be performed via the nose, mouth, or LMA under sedation and topical anesthesia or under general anesthesia. The nasal route may be preferred because it tends to maintain the scope in the midline, facilitating visualization of the larynx. Repeated practice in children with normal airways is recommended in order to acquire and maintain the skills essential to be proficient with the use of the FOB.

Fiberoptic-guided tracheal intubation can also be performed through a supraglottic airway device (SGA) (Figure 23.3) [28]. This technique is reported to have higher first attempt success rate than video-laryngoscopy (54% vs. 36%) in infants less than 1 year of age with difficult intubations; with no difference at older ages [33]. Once the SGA is



Figure 23.2 Direct laryngoscopy and video laryngoscopy blades demonstrating different angulations. From left to right: Miller 1 DL blade, Stortz C-Mac Miller 1VL blade (standard blades); Truview EVO, McGrath series 5 Mac 3 blade, King Vision VL blade, Storz C-Mac Pedi-D blade, Glidescope Cobalt AVL sheath, Glidescope Spectrum blade (all hyperangulated). (Source: Peyton et al. [32]. Reproduced with permission from Elsevier.)

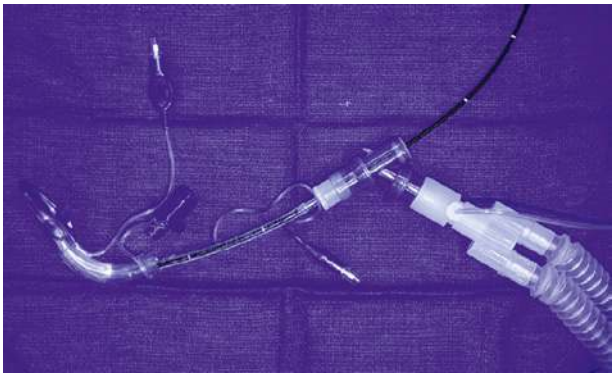


Figure 23.3 Supraglottic airway with endotracheal tube, bronchoscopic swivel adapter, and anesthesia circuit. (Source: Hsu & Fiadjoe [28]. Reproduced with permission from Cambridge University Press.)

appropriately positioned, the FOB is passed through the opening of the SGA into the trachea. An ETT is passed into the trachea over the FOB, which is then used to confirm appropriate positioning. When a standard ETT is used, only a short length of the ETT remains outside the SGA, making maintenance of ETT position and removal of the LMA difficult. A variety of techniques have been described to facilitate safe removal of the LMA while maintaining the ETT in place. First, a specially designed, long ETT can be placed over the FOB. Second, a tracheal tube exchange catheter (Cook Critical Care, Inc., Bloomington, IN) can be passed through the ETT into the trachea after which both the ETT and SGA are removed. An ETT is passed over the exchange catheter into the trachea. Third, the ETT can be made temporarily longer by wedging a half size smaller ETT into the proximal end, or by cutting the 15 mm adapter and using it to connect two ETTs of the same size together. After placement of the combined ETTs through the SGA, the SGA and proximal ETT are removed and the 15 mm adapter is replaced. Lastly, long forceps typically used for rigid bronchoscopy, can be used to hold the ETT while the SGA is removed. An alternative to fiberoptic intubation through the SGA, is "blind" passage of the ETT through the SGA into the trachea. Intubating SGAs have been developed for this purpose and are now available as smaller sizes. In younger children, the epiglottis frequently folds inside the SGA [34]. While this may not cause airway obstruction, traumatic injury to the epiglottis may occur from blind passage of an ETT.

Several other methods for controlling the airway of patients with a difficult airway have been described. These include the use of a lighted stylet, Combitube ® (esophageal tracheal airway), retrograde transtracheal intubation, blind nasal intubation, use of other specialized laryngoscopes with or without video capability, and digital (tactile) techniques. The reader is referred to a textbook of general pediatric anesthesiology for more detailed descriptions of these alternative techniques for intubation.

Emergency cricothyrotomy

In the rare instance in which mask ventilation and placement of an SGA do not provide adequate oxygenation and ventilation and tracheal intubation cannot be performed, percutaneous cricothyrotomy may be lifesaving. Percutaneous tracheotomy kits are available (Cook Critical Care, Inc., Bloomington, IN) that are designed to facilitate pediatric tracheotomy tube placement through the cricoid membrane using the Seldinger technique [35].

The difficult extubation

Tracheal extubation of patients with risk factors for difficult reintubation presents a challenge to the anesthesiologist and intensive care physician. Infants and children with congenital heart disease are at a high risk for adverse consequences associated with oxygen desaturation, hypercapnia, and hemodynamic instability prior to or during attempted reintubation. Respiratory distress signaling the need for reintubation may develop at a time when a physician with the greatest expertise in airway management is not immediately available, e.g., late at night. This can occur in the recovery room or intensive care unit, where equipment and other conditions may be less optimal than those encountered in the

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operating room. In addition, reintubation may be technically more difficult than the initial intubation due to airway edema, bleeding, secretions, and poor patient cooperation. Fiberoptic intubation or other alternative techniques may be extremely difficult or impossible under these circumstances.

Practice guidelines set forth by the American Society of Anesthesiologists Task Force for the Management of the Difficult Airway recommend that anesthesiologists have a preformulated strategy for extubating patients with a difficult airway [36]. This may include placement of a device through the indwelling ETT that serves as a stent over which the ETT can be replaced if the patient fails extubation. Accordingly, tracheal extubation of patients with a difficult airway has been performed over a guidewire, FOB, gum-elastic bougie, and a jet stylet [37–40].

Because of their relatively large outer diameter, airway exchange catheters are not suitable for use in infants or small children for maintenance of airway access following tracheal extubation. The smallest available Cook Airway Exchange Catheter (CAEC, Cook Medical, Bloomington, IN), for example, has a 3.0 mm outer diameter [41]. In infants, this may severely limit gas flow around the catheter during spontaneous breathing. For young children, the use of a 0.018″ guidewire for maintenance of airway access following tracheal extubation has been reported [44]. The guidewire used was Teflon™-coated and had a floppy, curved tip designed to minimize tissue trauma during placement. This guidewire facilitates placement of the smallest CAEC over which a 3.5 mm ID ETT may be advanced, a method similar to previously described reports [42, 43].

Airway and ventilatory management for thoracic surgery

Ventilation / perfusion in the lateral decubitus position

Several pediatric cardiovascular surgical procedures are performed in the lateral decubitus position, including patent ductus arteriosus (PDA) ligation, insertion of a systemic to pulmonary shunt, repair of coarctation of the aorta, and unifocalization of the pulmonary arteries. Significant ventilation-perfusion (V/Q) abnormalities may occur in this position under general anesthesia. During awake spontaneous breathing, ventilation is normally distributed preferentially to dependent regions of the lung so that there is a gradient of increasing ventilation from the most non-dependent to the most dependent lung segments. Because of gravitational effects, perfusion normally follows a similar distribution, with increased blood flow to dependent lung segments. Therefore, ventilation and perfusion are normally well matched. During thoracic surgery, several factors may act to adversely affect V/Q matching. First, general anesthesia, neuromuscular blockade, and mechanical ventilation cause a decrease in functional residual capacity of both lungs. In addition, compression of the dependent lung in the lateral decubitus position may cause atelectasis. In certain circumstances (e.g. patients with cardiomegaly and/or dextroposition of the heart), simple positioning in the decubitus position can cause the myocardial mass to compress or obstruct the airways. Meanwhile, retraction and/or single lung ventilation result in collapse of the operative lung. Hypoxic pulmonary vasoconstriction (HPV), which acts to divert blood flow away from the under-ventilated lung, thereby minimizing V/Q mismatch, may be diminished by inhalational anesthetic agents and other vasodilating drugs. These factors apply equally to infants, children, and adults.

The overall effect of the lateral decubitus position on V/Q mismatch, however, is unique in infants. In adults with unilateral lung disease, oxygenation is optimal when the patient is placed in the lateral decubitus position with the healthy lung dependent (“down”) and the diseased lung non-dependent (“up”) [44]. This is presumably related to an increase in blood flow to the dependent, healthy lung and a decrease in blood flow to the non-dependent, diseased lung due to the hydrostatic pressure (or gravitational) gradient between the two lungs. This phenomenon optimizes V/Q matching in the adult patient undergoing thoracic surgery in the lateral decubitus position.

In infants with unilateral lung disease, however, oxygenation is improved with the healthy lung “up.” [49]. Several factors account for this discrepancy between adults and infants. Infants have a soft, easily compressible rib cage that cannot fully support the underlying lung. Therefore, functional residual capacity is closer to residual volume, making airway closure likely to occur in the dependent lung even during tidal breathing [45]. When the adult is placed in the lateral decubitus position, the dependent diaphragm has a mechanical advantage, since it is “loaded” from abdominal pressure. This pressure is reduced in infants, thereby reducing the functional advantage of the dependent diaphragm. The infant’s small size also results in a reduced hydrostatic pressure gradient between the non-dependent and dependent lungs. Consequently, the favorable increase in perfusion to the dependent, ventilated lung is reduced in infants. This may be especially true for infants with systemic-to-pulmonary artery shunts, e.g., modified Blalock-Taussig, PDA, or multiple aorto-pulmonary collateral arteries (MAPCAs), in whom systemic pressure may be maintained in the pulmonary arterial circulation.

Finally, infants have increased oxygen consumption compared to adults, predisposing them to hypoxemia. Infants normally consume 6–8 mL of oxygen per kg/min compared with 2–3 mL/kg/min in the adult [46]. The functional residual capacity of the lung serves as an oxygen reservoir when ventilation ceases. An infant will more rapidly consume oxygen from the diminished oxygen reservoir that is produced during surgery in the lateral decubitus position. Infants with cyanotic congenital heart disease are at an increased risk of life-threatening oxygen desaturation during thoracic surgery.

Single-lung ventilation (SLV)

Prior to 1995, nearly all thoracic surgery in children was performed by thoracotomy. However, today many thoracic procedures can be performed using video-assisted thoracoscopic surgery (VATS). Reported advantages of VATS include smaller chest incisions, reduced postoperative pain, and more rapid postoperative recovery compared with thoracotomy [47–49]. VATS is now being utilized for PDA occlusion in some centers. Open thoracotomy is generally performed for more complex procedures, including repair of coarctation of the aorta and pulmonary artery unifocalization.

Single lung ventilation (SLV) is desirable during VATS as well as open thoracotomy because lung deflation improves visualization of thoracic contents and may reduce lung injury caused by the use of retractors. Because of the technical challenges and potential time-consuming nature of achieving SLV, especially in small children and infants, a discussion with the surgeon is important to determine whether SLV is necessary. May cardiothoracic operations can be accomplished successfully with a "pack and retract" technique that allows access to the posterior mediastinum and vascular structures, e.g., aorta and PDA. When SLV is deemed necessary, there are several different techniques that can be used in children.

Single lumen endotracheal tube (ETT)

The simplest means of providing SLV is to intentionally intubate the non-surgical mainstem bronchus with a conventional single lumen ETT. When the left bronchus is to be intubated, the bevel of the ETT is rotated 180° and the head turned to the right [50]. The ETT is advanced into the bronchus until breath sounds on the operative side disappear. A FOB may be passed through or alongside the ETT to confirm or guide placement. When a cuffed ETT is used, the distance from the tip of the tube to the proximal cuff must be shorter than the length of the bronchus so that the cuff is entirely in the bronchus [51]. This technique is simple and requires no special equipment other than a FOB and may be the preferred technique of SLV in emergency situations such as airway hemorrhage or contralateral tension pneumothorax.

Problems can occur when using a single lumen ETT for SLV. If a smaller, uncuffed ETT is used, it may be difficult to provide an adequate seal of the intended bronchus. This may prevent the operative lung from collapsing adequately, or fail to protect the healthy, ventilated lung from contamination by purulent or bloody material from the contralateral lung. It is not possible to suction the operative lung using this technique. Hypoxemia may occur due to obstruction of the upper lobe bronchus, especially when the short right mainstem bronchus is intubated. Microcuff® endotracheal tubes (Kimberly Clark, Roswell, GA) have a thinner walled cuff positioned near the tip of the endotracheal tube and therefore may be advantageous for use in SLV.

Variations of this technique have been described, including intubation of both bronchi independently with small ETTs [52–55]. One mainstem bronchus is initially intubated with an ETT, after which another ETT is advanced over a FOB into the opposite bronchus.

Balloon tipped bronchial blockers

A Fogarty embolectomy catheter or an end-hole, balloon wedge catheter may be used for bronchial blockade to provide single lung ventilation [56–59]. Placement of a Fogarty catheter is facilitated by bending the tip of its stylette toward the bronchus on the operative side. A FOB may be used to position the catheter and confirm appropriate placement. An example of a method for placing an end-hole catheter outside the ETT is intentional intubation of the bronchus on the operative side with an ETT. A guidewire is then advanced into that bronchus through the ETT. The ETT is removed and the blocker is advanced over the guidewire into the bronchus. An ETT is then reinserted into the trachea alongside the blocker catheter. The catheter balloon is positioned in the proximal mainstem bronchus under fiberoptic visual guidance or fluoroscopy. With an inflated blocker balloon the airway can be completely sealed, providing more predictable lung collapse and better operating conditions than with an ETT in the bronchus.

A potential problem with this technique is dislodgement of the blocker balloon into the trachea. The inflated balloon will then block ventilation to both lungs and/or prevents collapse of the operated lung. The balloons of most catheters currently used for bronchial blockade have low volume, high pressure properties and over-distension can damage or even rupture the airway [60]. It has been reported, however, that bronchial blocker cuffs produced lower "cuff to tracheal" pressures than double lumen tubes [61]. When closed tip bronchial blockers are used, the operative lung cannot be suctioned and continuous positive airway pressure (CPAP) cannot be provided to the operative lung if needed.

Adapters are available that facilitate ventilation during placement of a bronchial blocker through an indwelling ETT [62, 63]. A 5 French endobronchial blocker that is suitable for use in children with a multiport adapter and FOB is commercially available (Cook Critical Care, Inc., Bloomington, IN) [64]. The risk of hypoxemia during blocker placement is diminished and repositioning of the blocker may be performed with fiberoptic guidance during surgery. Even with use of an FOB with a diameter of 2.2 mm, however, the indwelling ETT must be at least 4.5 mm ID to allow passage of the catheter and FOB. The use of this technique, therefore, is generally limited to children over the age of 18 months. Even in toddlers and children, passage of a suction catheter alongside the blocker catheter may be difficult.

Univent tube

The Univent™ tube (Fuji Systems Corporation, Tokyo, Japan) is a conventional ETT with a second lumen containing a small tube that can be advanced into a bronchus [65–67]. A balloon located at the distal end of this small tube serves as a blocker. Univent™ tubes require a FOB for successful placement. Univent™ tubes are available in sizes as small as a 3.5 and 4.5 mm ID for use in children over six years of age [68]. Because the blocker tube is firmly attached to the main ETT, displacement of the Univent™ blocker balloon is less likely than when other blocker techniques are used. The blocker tube has a small lumen which allows egress of gas and can be used to insufflate oxygen or suction the operated lung, but this feature is only present in size 6.0 and larger Univent™ tubes.

A disadvantage of the Univent™ tube is the large amount of cross sectional area occupied by the blocker channel, especially in the smaller size tubes which have a disproportionately high resistance to gas flow [69]. The Univent™ tube's blocker balloon has low volume, high pressure characteristics so mucosal injury can occur during normal inflation [70, 71].

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Double lumen tubes (DLTs)

All DLTs are essentially two tubes of unequal length molded together. The shorter tube ends in the trachea and the longer tube in the bronchus. DLTs for older children and adults have cuffs located on the tracheal and bronchial lumens. The tracheal cuff, when inflated, allows positive pressure ventilation. The inflated bronchial cuff allows ventilation to be diverted to either or both lungs and protects each lung from contamination from the contralateral side.

The smallest cuffed DLT is 26 Fr (Rusch, Duluth, GA), and may be used in children as young as 8 years old. The lumens of this DLT are small in diameter, and therefore, passage of a FOB or suction catheter is limited. DLTs are also available in sizes 28 and 32 Fr (Mallinckrodt Medical, Inc., St. Louis, MO) suitable for children 10 years and older.

DLTs are inserted in children using the same technique as in adults [72]. The tip of the tube is inserted just past the vocal cords and the stylet is withdrawn. The DLT is rotated 90 degrees to the appropriate side and then advanced into the bronchus. In the adult population the depth of insertion is directly related to the height of the patient [73]. No equivalent measurements are yet available in children. If fiberoptic bronchoscopy is used to confirm tube placement, a scope with a small diameter and sufficient length must be available [74].

A DLT offers the advantage of ease of insertion as well as the ability to suction and oxygenate the operative lung with CPAP. Left DLTs are preferred to right DLTs because of the shorter length of the right main bronchus [75]. Right DLTs are more difficult to position accurately because of the greater risk of right upper lobe obstruction.

DLTs are safe and relatively easy to use. There are very few reports of airway damage from DLTs in either adult or pediatric patients. Their high volume, low pressure cuffs should not damage the airway if they are not overinflated with air or distended with nitrous oxide while in place. In a study of 30 children aged 5 months-18 years with a median weight of 28 kg undergoing SLV with various devices including DLTs and bronchial blockers, the intracuff pressures in the tracheal and bronchial cuffs were measured [76]. Median tracheal cuff pressure was 32 cm H_2O (range 11–90), median bronchial cuff pressure 44 cm H_2O (range 10–100), and 65% of tracheal cuffs and 70% of bronchial cuffs had pressure exceeding the recommended 30 cm H_2O. A higher rate of overinflation was seen with bronchial blockers, vs. DLT or selective bronchial intubation. There were no clinical complications in the study, but the authors advised inflating the cuffs carefully and considering pressure monitoring of inflated cuffs.

Guidelines for selecting appropriate tubes (or catheters) for SLV in children are shown in Table 23.5. There is significant variability in overall size and airway dimensions in children, particularly in teenagers. The recommendations shown in Table 23.5 are based on average values for airway dimensions. Larger DLTs may be safely used in large teenagers.

Table 23.5 Tube selection for single-lung ventilation in children

Age (years)	ETT (ID mm)[a]	BB[b] (Fr)	Univent™[c]	(ID mm) DLT (Fr)[d]
0.5–1	3.5–4.0	5		
1–2	4.0–4.5	5		
2–4	4.5–5.0	5		
4–6	5.0–5.5	5		
6–8	5.5–6	6	3.5	
8–10	6.0 cuffed	6	3.5	26
10–12	6.5 cuffed	6	4.5	26–28
12–14	6.5–7.0 cuffed	6	4.5	32
14–16	7.0 cuffed	7	6.0	35
16–18	7.0–8.0 cuffed	7	7.0	35

[a] Sheridan Tracheal Tubes, Kendall Healthcare, Mansfield, MA, USA.
[b] Arrow International Corp., Redding, PA, USA.
[c] LMA North America, San Diego, CA, USA.
[d] 26 Fr (Rusch, Duluth, GA, USA); 28–35 Fr (Mallinckrodt Medical, Inc., St. Louis, MO, USA).
ID, internal diameter in mm, Fr, French size, DLT, double-lumen tube.

Recent data concerning bronchial diameters and single lung ventilation in small children

In recent years, additional data about bronchial diameters in young children have become available through high resolution CT scanning and have informed selection criteria for sizes of bronchial blockers, double lumen ETTs, and other devices. One scheme is displayed in Table 23.6 [77]. In smaller children less than 2 years of age, extraluminal placement of a bronchial blocker is the only viable technique (besides endobronchial intubation) to provide SLV because of the small diameter of the ETT relative to the blocker catheter and FOB utilized for placement. Larger children who can accept a 5.0 mm ID ETT or larger are candidates for intraluminal blocker placement (Figure 23.4). Approaches to place the extraluminal bronchial blocker in small children include the "bending the rules" approach (Figure 23.5), and the intra-to extraluminal approach (Figure 23.6).

Table 23.7 summarizes the strategies for SLV in infants and young children, with the advantages and disadvantages of each method [80].

Ventilatory management during thoracic surgery

During two-lung ventilation, tidal volumes of 6–8 mL/kg are typically used at a respiratory rate that provides normocapnia. When one lung is ventilated, the delivered tidal volume should be reduced to 4–5 mL/kg, and the respiratory rate increased in order to avoid excess inspiratory pressure to the ventilated lung. Pressure control ventilation can also be used, in which case attention must be directed at tidal volumes, which may be decreased with manipulation of the thoracic contents. Pulse oximetry and capnography reflect trends in the changes in oxygenation and ventilation but monitoring of arterial blood gas tensions is important to accurately determine PaO_2 and $PaCO_2$ during single lung ventilation in infants and children with congenital cardiac disease. Hypercapnia and hypoxemia may cause a reduction in cardiac output, as may hyperinflation of the ventilated lung.

Hypoxemia is commonly encountered during thoracic surgical procedures, especially in children with CHD and preexisting hypoxemia, impaired myocardial function, and/or pulmonary hypertension. Hypoxemia develops from one or

Table 23.6 Age and device selection for OLV in infants and young children

Age	Mainstem Bronchus Diameter (mm)[a]		Standard UC ETT Size for Endobronchial Intubation (OD mm)[b]		Standard C ETT Size for Endobronchial Intubation (OD mm)[b]		5F Arndt	7F Arndt	9F Arndt	3F	4F	5F	9F	EZ-	3.5	4.5	26F
	R	L	R	L	R	L	BB	BB	BB	Fogarty	Fogarty	Fuji	Fuji	Blocker	Univent	Univent	DLT
0–3 months	4.4[a]	3.6[a]	3.0 (4.2)	2.5 (3.6)	3.0 (4.3)	-	E	-	-	E	E	E	-	-	-	-	-
3–6 months	4.7[a]	3.9[a]	3.0 (4.2)	2.5 (3.6)	3.0 (4.3)	-	E	-	-	E	E	E	-	-	-	-	-
6–12 months	5.4[a]	4.2[a]	3.5 (4.9)	3.0 (4.2)	3.5 (4.9)	3.0 (4.3)	E	-	-	E	E	E	-	-	-	-	-
1–2 years	5.4[c]	5.6[c]	4.0 (5.5)	3.5 (4.9)	4.0 (5.6)	3.5 (4.9)	E	-	-	E	E	E	-	-	-	-	-
2–4 years	7.5[c]	6.6[c]	4.5 (6.2)	3.5 (4.9)	4.5 (6.2)	3.5 (4.9)	E/I	E	-	E/I	E/I	E/I	-	-	-	-	-
4–6 years	8.3[c]	7.3[c]	4.5 (6.2)	4.0 (5.5)	4.5 (6.2)	4.0 (5.6)	E/I	E	-	E/I	E/I	E/I	-	-	-	-	
6–8 years	8.9[c]	7.8[c]	5.5 (7.5)	5.0 (6.9)	5.5 (7.5)	5.0 (6.9)	E/I	E/I	-	-	-	E/I	-	E	+	-	-
8–10 years	9.9[c]	8.8[c]	-	-	6.0 (8.2)	5.0 (6.9)	-	E/I	E/I	-	-	-	E/I	E/I	+	+	+

Summary of bronchial diameters and recommended lung isolation device or ETT size for lung isolation. ETT outer diameters can vary significantly by manufacturer, so care must be taken to evaluate the outer diameter of a given ETT when planning to use it for endobronchial intubation and OLV.

Abbreviations: BB, bronchial blocker; C, cuffed; CT, computerized tomography; DLT, double-lumen tube; E, extraluminal; ETT, endotracheal tube; Fuji, Fuji Uniblocker; I, intraluminal; L, left; OD, outer diameter; OLV, one-lung ventilation; R, right; UC, uncuffed.

[a] Median bronchial diameter measured by high resolution CT (Downard MG, Johnson AL, Heald CJ, Anthony EY, Singh J, Templeton TW, unpublished data, April 2019).

[b] Measurement of outer diameter is for Shiley endotracheal tubes.

[c] Median bronchial diameter measured by high resolution CT.

Source: Reproduced with permission from Templeton et al. [77].

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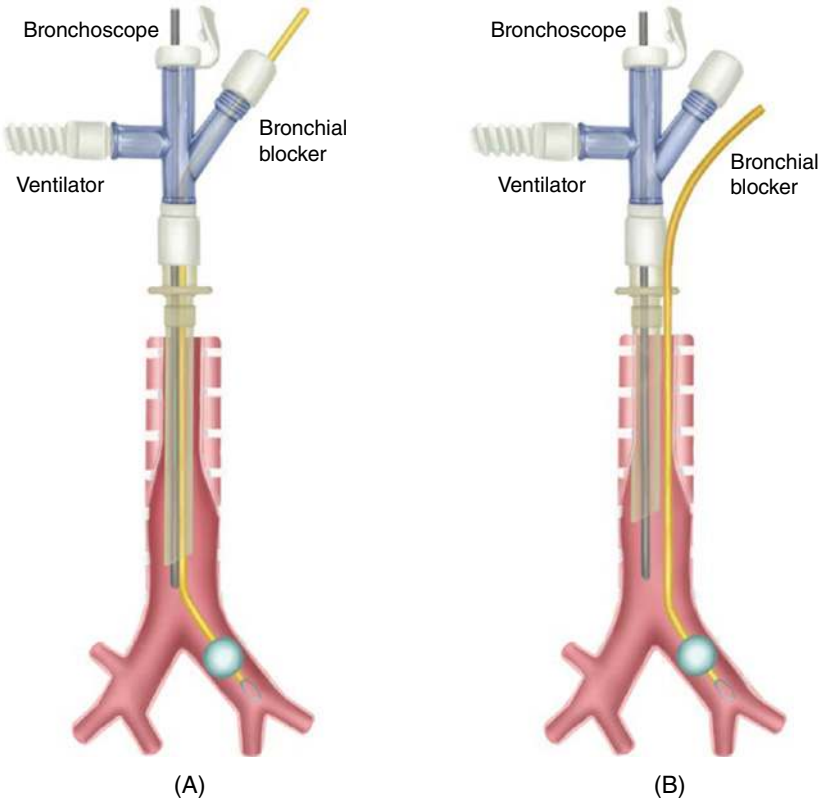


Figure 23.4 Intraluminal versus extraluminal approach to bronchial blocker placement. A, Intraluminal approach with fiberoptic scope and bronchial blocker inserted through the multiport adapter with both devices present within the endotracheal tube. B, Extraluminal bronchial blocker with blocker present outside of the endo- tracheal tube within the airway and the fiberoptic scope inserted through the multiport adapter and endotracheal tube to facilitate placement. (Source: Templeton et al. [82]. Reproduced with permission from Wolters Kluwer Health, Inc.)

more possible mechanisms. The conducting passages of the operative lung are intentionally obstructed during single-lung ventilation and/or from surgical retraction and compression of the operative lung. Secretions in the airways as well as surgical and hydrostatic compression may also compromise gas flow through the conducting passages of the dependent lung. The reduction in ventilation to the operative lung produces regional hypoxemia that induces hypoxic pulmonary vasoconstriction (HPV), which will reduce ventilation/perfusion (V/Q) mismatch. However, HPV may be impaired in children with CHD. It has been shown in a dog model that HPV is impaired by elevated pulmonary arterial pressure and by low mixed venous oxygen tension, both of which are commonly encountered among children with CHD [78, 79]. Retraction of the operative lung may compress the mediastinum, impairing cardiac filling and reducing cardiac output These changes, in turn, cause a decrease in mixed venous oxygen concentration and exacerbate hypoxemia from intracardiac and/or intrapulmonary shunting.

Severe hypoxemia should be treated immediately by increasing the FiO_2 to 1.0 and by confirming patency of the ETT. A suction catheter should be passed through the ETT to clear secretions and/or blood from the lumen. Irrigation with sterile saline may be beneficial. If the ETT remains occluded, an FOB may be used to determine the site of obstruction and to reestablish patency of the ETT. The surgeon should be informed, and compression of the lung and/or mediastinum should be minimized. Administration of intravenous fluids may improve cardiac output and improve V/Q matching by increasing perfusion pressure to the lungs. Application of continuous positive airway pressure (CPAP) with 100% O_2 to the non-dependent lung will reduce intrapulmonary shunt and improve oxygenation during SLV. If hypoxemia persists despite these maneuvers, the operative lung should be re-inflated with 100% oxygen. Although nitric oxide might be expected to increase pulmonary blood flow to the ventilated lung and improve oxygenation, two studies in adults failed to show benefit from nitric oxide during SLV [80, 81].

Some degree of hypoxemia is expected during SLV. In a study of 52 children without CHD undergoing SLV during VATS, a decrease in SpO_2 occurred in 40% of patients in whom a bronchial blocker was used [82]. The bronchial blockers used did not have lumens for administration of CPAP/ O_2. Forty percent of patients in this study also had $PaCO_2$ values >50 mmHg, although the clinical significance of hypercarbia was not documented. In another study of 12 pediatric patients in whom VATS was performed for closure of patent ductus arteriosus, CO_2 insufflation and hypercarbia ($PaCO_2$ 50–70 mmHg) were not associated with circulatory impairment [83]. In fact, the authors reported that hypercarbia was associated with increased cardiac output and central venous and arterial O_2 tension in these patients. The specific mechanism of these effects of hypercarbia, e.g., changes in Qp:Qs, were not described.

Changes in lung function in children with CHD

Ventilation may be impaired in children with increased pulmonary blood flow due to left-to-right shunts. Both decreased lung compliance and increased airway resistance have been demonstrated in these children. Two studies in infants and young children with CHD found strong correlation between echocardiographic evidence of pulmonary artery engorgement and decreased lung compliance [84, 85]. A study of neonatal patients undergoing thoracotomy for Blalock-Taussig (BT) shunt placement or repair of coarctation of the aorta [86] determined that lung compliance decreased and airway resistance significantly increased after surgery. The return to baseline pulmonary function was prolonged after BT shunt placement when compared with coarctation repair, suggesting that an increase in pulmonary blood flow worsens pulmonary mechanics [86]. Some infants develop substantial increases in total lung resistance following heart surgery, the severity of which can be predictive of postoperative respiratory failure [87]. Acute increases in pulmonary artery pressure also produce significant changes in lung mechanics. One study demonstrated that airway resistance increases 43% and compliance decreases 11% during periods of acute pulmonary hypertension [88]. In this study, lung biopsy specimens from patients with the greatest increase in pulmonary artery pressure had increased bronchial smooth muscle mass, suggesting that the same local mediators that affect increases in pulmonary arterial pressure also may cause bronchospasm. Changes in lung mechanics correlate better with the magnitude of pulmonary vascular engorgement than with pulmonary artery hypertension. During cardiac catheterization, the degree of increased pulmonary blood flow is proportionate to increases in respiratory resistance among infants who are mechanically ventilated [89]. Infants with CHD and pulmonary overcirculation have reduced dynamic compliance and increased respiratory resistance that often improves following surgery [90].

Extrinsic compression of larger airways by the heart and vascular structures can also affect lung function in children with CHD. Both left and right mainstem bronchial compression have been described from enlarged pulmonary arteries. An enlarged left atrium can compress the left mainstem bronchus, and bronchial compression can occur from extrinsic compression by a right ventricle-to-pulmonary artery conduit [91].

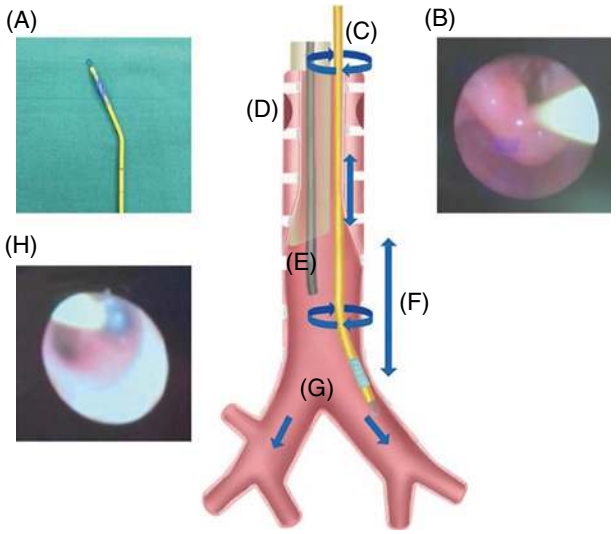


Figure 23.5 Summary of "Bending the Rules" approach for extraluminal placement for bronchial blocker placement. (A) Arndt bronchial blocker prepared with 30°–45° bend. (B) Extraluminal 5F Arndt bronchial blocker in glottis before placement of endotracheal tube. (C) Bronchial blocker is manipulated using a twisting motion at the oral aperture to direct the distal tip. (D) Sealing pressure at cricoid should be between 17 and 24 cm H_2O to allow for cephalad/caudad translocation of the bronchial blocker. (E) Endotracheal tube with fiberoptic scope inside. (F) Note the increased distance from end of endo tracheal tube to carina to facilitate visualization and manipulation of blocker within the airway. (G) Bronchial blocker is advanced into the desired mainstem bronchus distal to the carina. (H) Bronchial blocker occlusive balloon is infated under direct vision once patient is in the final position. (Source: Templeton et al. [82]. Reproduced with permission from Wolters Kluwer Health, Inc.)

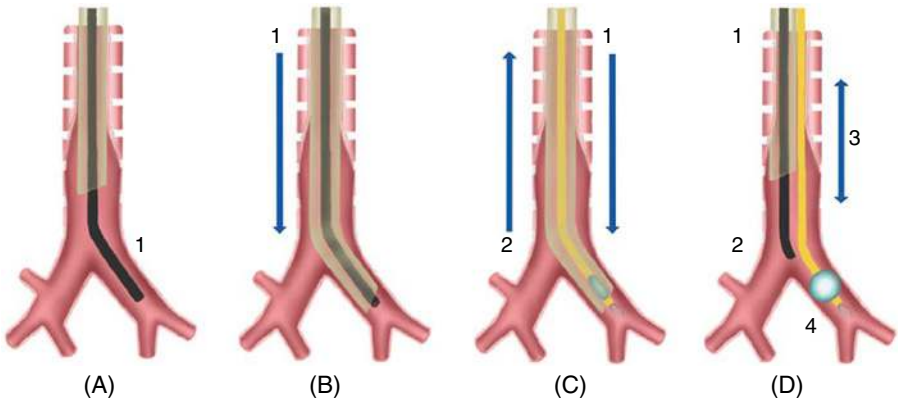


Figure 23.6 Schematic summary of intra- to extraluminal approach to bronchial blocker placement. (A) 1: Fiberoptic scope passed through the endotracheal tube into the left mainstem bronchus. (B) 1: Endotracheal tube railroaded over flexible fiberoptic into the desired mainstem bronchus. (C) 1: Bronchial blocker threaded into the endotracheal tube. 2: Endotracheal tube removed leaving the bronchial blocker in place. (D) 1: Repeat direct laryngoscopy and second endotracheal tube placed adjacent to the bronchial blocker in the glottis. 2: Fiberoptic scope inserted into endotracheal tube. 3: Bronchial blocker depth adjusted. 4: Occlusive balloon is inflated under direct vision in the left mainstem bronchus. (Source: Templeton et al. [82]. Reproduced with permission from Wolters Kluwer Health, Inc.)

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Table 23.7 Summary of strategies for SLV in infants and young children

Strategy for OLV	Appropriate Age	Advantages	Disadvantages
Endobronchial intubation	<5 years	• Easy to perform • No special blocker or tube required • Can be performed blindly, with fiberoptic assistance or under fluoroscopy • Good quality isolation • Technique of choice in young children with a difficult airway	• Difficult to change to two-lung ventilation • ETT can become occluded with blood and/or secretions • Easy to occlude right upper lobe bronchus with right-sided endobronchial intubation • Inability to suction nonventilated lung or apply CPAP
Bronchial blocker	All age groups	• High quality of isolation • Rapidly change from OLV to two-lung ventilation • Appropriate for all ages depending on size and type of blocker • Intra or extraluminal use • Appropriate for children with a tracheostomy • Can be used in combination with a supraglottic airway	• Can be technically challenging to position • CPAP to nonventilated lung may be ineffective • Can be easily dislodged as a result of surgical manipulation
Univent tube	>8 years	• High quality of isolation • May be more positionally stable than a bronchial blocker • Easy to change from OLV to two-lung ventilation	• Appropriate for children ≥8 years of age • Smaller ventilating lumen relative to patient size may lead to increased resistance
Double lumen tube	>8 years	• Usually straight forward to position • High quality of isolation • Positionally stable • Easy to change from OLV to two-lung ventilation • Can suction and apply CPAP to nonventilated lung	• Appropriate for children ≥8 years of age • Potentially increased rates of glottic or tracheal injury • Not appropriate in most children with a difficult airway

CPAP, continuous positive airway pressure; ETT, endotracheal tube; OLV, one lung ventilation.
Source: Templeton et al. [82]. Reproduced with permission from Wolters Kluwer Health, Inc.

Changes in lung function from CPB

Pulmonary dysfunction is common after cardiac surgery [92]. Children with increased pulmonary blood flow due to left-to-right shunting may develop up to a three-fold increase in lung water in the immediate post-operative period, the degree of which appears to be related to the presence of pulmonary hypertension [93, 94]. In addition, both quantitative and qualitative differences in surfactant have been described in children after CPB [95]. Others have found that the most common adverse pulmonary effect of CPB is the development of atelectasis, reported to be as high as 82% among children undergoing CPB [96]. Both noncardiogenic pulmonary edema and acute bronchospasm have also been reported following CPB in children and adults, [97, 98] although the incidence of these complications in children is unknown. Some authors found correlation between the duration of CPB and the severity of lung injury while others found only minor changes in pulmonary mechanics related to CPB [90, 99–101]. These differences may be related to improvements in CPB management over the past decade. A study of over 100 infants undergoing heart surgery found no correlation between the duration of CPB, the duration of aortic cross clamp, the use of deep hypothermic circulatory arrest, and pulmonary outcomes [102].

Cardiopulmonary interactions

Positive intrathoracic pressure typically has adverse hemodynamic effects on the right ventricle and variable hemodynamic effects on the left ventricle in patients with normal cardiac anatomy and function. Intrathoracic pressure is transmitted to the thin-walled, compressible superior and inferior venae cavae, reducing venous blood return to the right atrium and leading to a decrease in right ventricular filling [103]. In addition, right ventricular output will decrease if pulmonary vascular resistance (PVR) increases from hyperinflation of the lungs. With acute rises in PVR, the right ventricle may become dilated, resulting in decreased left ventricular filling as the intraventricular septum is displaced to the left [104].

PVR is affected by mechanical factors, chemical factors, and local humoral factors. PVR is optimal when the resting lung volume is at functional residual capacity (FRC) and becomes elevated when lung volumes are above or below FRC. As lung volume decreases below FRC extra-alveolar (large) blood vessels are compressed. In addition, atelectasis develops when lung volume decreases, leading to hypoxic pulmonary vasoconstriction with associated elevation in PVR. When lung volumes exceed FRC, alveolar distension causes compression of smaller arterioles and

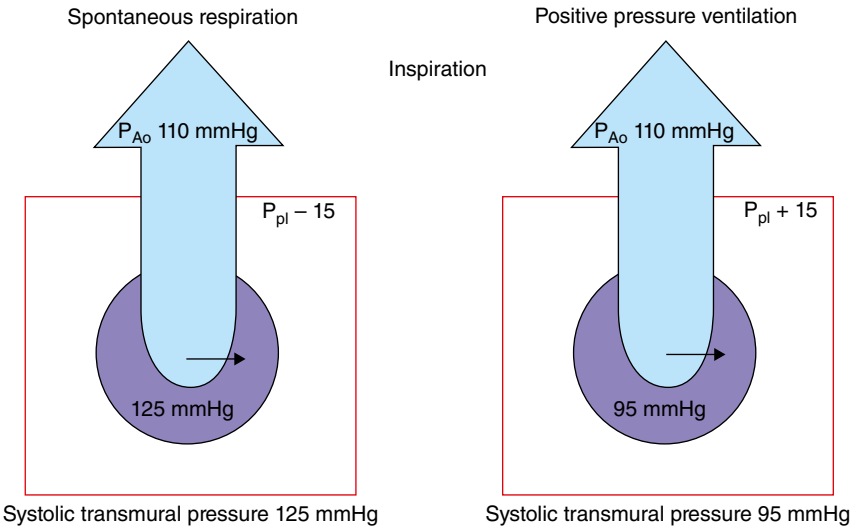


Figure 23.7 The effect of positive pressure ventilation on systemic ventricular transmural pressure. P_{Ao}, aortic pressure; P_{pl}, pleural pressure.

capillaries, also resulting in an increase in PVR [105] (Figure 23.2). Both oxygen tension and pH have significant effects on PVR [106], with alveolar hypoxemia and acidemia causing an increase in PVR; alkalemia causes a reduction in PVR. Local pH has the greatest effect on pulmonary vascular tone, and PVR is reduced by producing either respiratory or metabolic alkalemia. Finally, lung expansion from positive pressure ventilation causes a local release of prostaglandins, leading to pulmonary vasodilation. This may explain the decrease in PVR associated with the onset of hyperventilation that occurs before CO_2 is reduced [106].

Changes in pleural pressure also affect left ventricular function. Ventricular output is affected by changes in afterload of the ventricle from transmitted intrathoracic pressure to the ventricular wall. The left ventricle lies within the thoracic cavity whereas most of the systemic arterial tree lies outside the thoracic cavity. Therefore, changes in pleural pressure affect the left ventricle and not the systemic vasculature. Afterload is affected by the ventricular transmural pressure i.e., the intracavitary pressure minus the pleural pressure. During spontaneous ventilation, negative intrapleural pressure is transmitted to the ventricular wall. During systole, the ventricle must overcome systemic vascular resistance and pleural pressure; therefore, afterload is increased when negative pleural pressure develops as occurs during spontaneous ventilation. With positive pressure ventilation, systemic vascular resistance is unchanged, but afterload to the ventricle is reduced because positive intrapleural pressure reduces ventricular transmural pressure [107–109] (Figure 23.7).

Mechanical ventilation for children with CHD

Changes in pleural pressure during inspiration have a variety of hemodynamic effects on patients with cardiac and/or pulmonary disease. In healthy individuals, spontaneous inspiration augments venous return and increases right ventricular output while increasing left ventricular afterload and decreasing left ventricular output. The net effect on total cardiac output is minor, and the conversion to positive pressure ventilation will have minimal effects on cardiac output. However, in hypovolemic patients cardiac output decreases from positive pressure ventilation because the decrease in right ventricular preload produces the predominant hemodynamic effect.

In patients with significant right heart dysfunction, mechanical ventilation parameters should be selected that will minimize intrathoracic pressure, maintain lung volume at FRC, avoid hypoxemia, and optimize pH in order to minimize PVR. Intrathoracic pressure should be minimized by avoiding excess positive end-expiratory pressure (PEEP) and excessively large tidal volumes. Again, it should be emphasized that lung volumes *below FRC* will also lead to an increase in PVR. Thus, PEEP should be titrated to achieve physiologic FRC throughout the operative case. Pressure volume loops can be used to optimize pulmonary mechanics (Figure 23.8). Hyperventilation is the traditional maneuver performed to reduce PVR because the associated hypocarbia produces alkalemia. However, both metabolic and respiratory alkalosis reduce pulmonary vascular resistance [106, 110]. Local tissue pH is the most significant factor affecting tone in pulmonary vessels. Because hyperventilation requires an increase in minute ventilation, greater intrathoracic pressure must be used which may reduce right ventricular preload. Creating a metabolic alkalosis through the administration of sodium bicarbonate will produce the same beneficial effect on reducing PVR without interfering with right ventricular filling. Inhaled nitric oxide or high concentrations of inhaled oxygen may further reduce PVR in patients with pulmonary hypertension and will improve right heart output.

Acute increases in PVR often produce profound systemic hypotension because left ventricular filling is significantly impaired from both a reduction in preload (right heart output) and a leftward shift of the intraventricular septum as the right heart dilates. Diastolic hypotension reduces coronary

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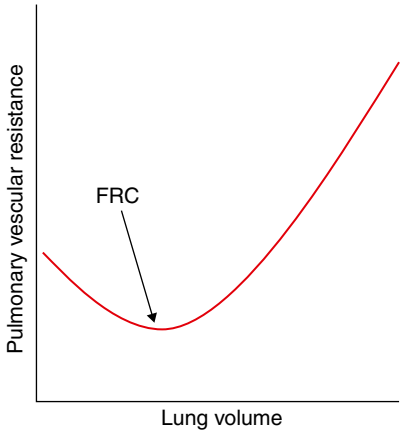


Figure 23.8 Relationship of lung volume to pulmonary vascular resistance. FRC, functional residual capacity.

perfusion to a stressed myocardium which may rapidly result in cardiovascular collapse.

Positive pressure ventilation improves cardiac output among patients with left ventricular systolic failure [111, 112]. As the left ventricle fails and begins to dilate, left atrial pressure is increased, leading to pulmonary venous congestion and decreased lung compliance. Work of breathing is increased and greater negative pressure is generated during spontaneous ventilation, which, in turn, increases left ventricular afterload. Positive pressure ventilation may decrease the work of breathing and thereby decrease oxygen consumption. In addition, positive intrathoracic pressure will reduce ventricular afterload, enhancing cardiac output. However, patients with diastolic ventricular dysfunction will have small stroke volumes as their stiff, hypertrophied myocardium does not adequately relax. The reduction in preload from positive pressure ventilation produces the predominant effect on cardiac output. Studies on patients with tetralogy of Fallot, who commonly have right ventricular diastolic dysfunction, show that cardiac output increases with negative pressure ventilation [113].

Patients with non-pulsatile pulmonary blood flow (e.g., following bidirectional cavopulmonary anastomoses and Fontan procedures) show the most dramatic interactions between alterations in intrathoracic pressure, pulmonary blood flow, and cardiac output. Because they lack pulsatile flow in their pulmonary arteries, positive intrathoracic pressure interferes with pulmonary blood flow in these patients. Likewise, elevations in PVR reduce pulmonary blood flow. Reductions of pulmonary blood flow impair ventricular filling and reduce cardiac output. Maintenance of physiologic FRC and use of small tidal volumes is critical in these patients. PEEP is commonly avoided in Glenn and Fontan patients in order to diminish intrathoracic pressure. However, atelectasis and lung volumes below FRC will increase PVR and these changes can be minimized through the use of PEEP. Delivering the appropriate amount of PEEP during mechanical ventilation of patients with single ventricle physiology is warranted.

Negative pressure ventilation produces a significant improvement in stroke volume and pulmonary blood flow over that of conventional positive pressure ventilation [114]. High-frequency jet ventilation effectively reduces $PaCO_2$ at a lower mean airway pressures than conventional mechanical ventilation and has been shown to improve cardiac output when compared to conventional ventilation in postoperative Fontan patients [115].

In patients with lung disease associated with collapsed or fluid filled alveoli (atelectasis, pulmonary edema, pneumonia, ARDS) gas exchange improves when FRC is re-established through the use of PEEP. The application of PEEP has variable cardiovascular effects depending on lung compliance. Even high levels of PEEP have limited effect on cardiac output when lung compliance is reduced, because the higher airway pressures are not transmitted to the heart and pulmonary vasculature [116]. Some congenital heart defects such as tetralogy of Fallot with absent pulmonary valve are associated with small and large airway compression from engorged pulmonary arteries. These patients develop airway collapse during exhalation and typically manifest hyperinflation of some lung segments and atelectasis in other areas [117]. Such children benefit from a ventilatory strategy that increases exhalation time, i.e., a slower ventilatory rate. Optimal levels of PEEP can be determined by pressure-volume and flow-volume loops (Figure 23.8). Similarly, patients with left-sided obstructive lesions such as mitral valve stenosis, hypertrophic/obstructive cardiomyopathy, and/or aortic stenosis are at risk for the development of significant pulmonary edema secondary to left atrial hypertension. Increased left atrial pressure can limit pulmonary venous drainage, prompting hydrostatic extrusion of fluid into the pulmonary interstitium and air spaces. While ventilatory strategies may not completely relieve the left-sided obstruction, patients will benefit both from the restoration of FRC through the use of PEEP and from the reduction in left ventricular afterload with carefully titrated positive pressure ventilation.

Lung management during CPB

Studies performed in animal models and adult patients have compared use of continuous mechanical ventilation, intermittent sigh breaths, and CPAP during CPB. Most studies show improvement in postoperative gas exchange with CPAP; however, this difference appears to be short-lived [118, 119]. No such studies have been performed in children. Because closing capacity is higher in infants, maintaining airway patency through the application of CPAP would theoretically be beneficial. Lung inflation from CPAP, however, may interfere with adequate surgical access to the heart and complete lung collapse is usually required. An FiO_2 of 0.21 versus 1.0 has the theoretical benefit of diminishing absorption atelectasis during CPB, although this also has not been studied in children. Before weaning from CPB and after confirmation of the absence of air in the left atrium and ventricle, vital capacity breaths should be administered in order to re-establish patency of collapsed airways and alveoli [120] and to mobilize retained secretions. The tracheal tube should be suctioned prior to weaning from CPB to assure patency of the tracheal tube and large airways, but care must be taken in order to avoid tracheal mucosal injury producing hemorrhage in a fully anticoagulated patient. Inhaled beta-2 agonists are often administered before weaning from CPB in order to decrease airway reactivity; however, the efficacy of this practice has not been proven.

Volume control vs. pressure control ventilation

Volume-limited (volume control) ventilation delivers a relatively constant tidal volume despite changes in total pulmonary compliance. During volume-controlled ventilation the peak inspiratory pressure varies and is dependent on the set tidal volume, PEEP, gas flow rate, gas flow resistance, and respiratory system compliance. The presence of high inflation pressures signals decreased pulmonary compliance or conductance (e.g., offset of neuromuscular blockade, bronchospasm) or obstruction of the breathing circuit (e.g., occluded ETT). Disadvantages of volume-limited ventilation include the potential to produce very high inflating pressures and increase the risk of barotrauma. With proper monitoring of inspiratory pressure, including the use of appropriate limits and alarms, changes in the patient's pulmonary mechanics can be observed and the risk of barotrauma minimized. Because of technical difficulties in accurately delivering very small tidal volumes (e.g., <100 cc), volume-limited ventilators have been primarily used in patients over 10 kg body weight. More recently, however, ventilators have been introduced that may safely be used in a volume-limited mode for smaller patients, i.e., with a low incidence of hypoventilation as well as volutrauma [121, 122].

In the neonate and infant, anesthesia ventilators that are pressure-limited and time-cycled are commonly used. These ventilators offer the advantages of avoiding excessive inflating pressures and barotrauma. However, a decrease in the compliance or conductance of the patient's respiratory system, ventilator circuit, or tracheal tube will cause a reduction in delivered tidal volume. An increase in compliance, conversely, will result in an increased tidal volume and the risk of volutrauma. Pressure limited or pressure control ventilation (PCV) is frequently applied to infants and children receiving mechanical ventilatory support in which severe pulmonary pathology dictates the need for rapid respiratory rates or high inflating pressures. Advantages of this mode of ventilation include limiting the peak inflating pressure delivered by the ventilator, thereby limiting the trans-alveolar pressure and ventilator-induced lung injury [123]. The decelerating flow used during PCV is thought to improve the distribution of gas flow to the lungs [124]. When compared with volume control ventilation there is a more rapid improvement in lung compliance and oxygenation with PCV [125]. Older anesthesia ventilators may not deliver small tidal volumes accurately because of the proportionately large compression volume loss in the ventilator and circuit [126]. Therefore, setting an anesthesia ventilator in pressure control mode will deliver more consistent ventilation to infants when the anesthesia machine cannot compensate for compression volume loss in the entire circuit [122]. Modern anesthesia ventilators are capable of delivering accurate tidal volumes down to 20 mL.

Monitoring ventilation

Ventilation is the tidal exchange of gas between lungs and the atmosphere and is reflected in the concentration of CO_2 in arterial blood ($PaCO_2$). In the operating room, the most common non-invasive method of measuring CO_2 is capnography, which closely reflects changes in $PaCO_2$ among patients without lung or heart disease. Capnography is less accurate in infants when there is a leak around the ETT and when CO_2 is measured at the Y piece due to fresh gas washout of the small volume of gas sampled [127]. Another measurement of alveolar ventilation is the measurement of exhaled tidal volumes (V_T). Exhaled V_T is usually measured by a spirometer located at the end of the expiratory limb. This measurement overestimate actual V_T because it reflects the patient's exhaled V_T as well as the compression volume in the breathing circuit. However, modern anesthesia ventilators subtract the compression volume and provide a V_T measurement that is accurate unless there is a large leak in the circuit. A leak around the ETT will produce an underestimate the actual exhaled gas volume. As stated earlier in the chapter, the use of cuffed endotracheal tubes allows safer, more accurate delivery and assessment of mechanical ventilation in infants. Because end-tidal CO_2 may significantly underestimate arterial CO_2 due to dead space ventilation, particularly in patients with reduced pulmonary blood flow, blood gases should be measured frequently in order to assure adequate ventilation and to monitor changes in acid-base status.

Anesthesia ventilators

When using volume-controlled ventilation, the goal of modern ventilator designs is to deliver a volume to the patient that is as close as possible to the volume set to be delivered. To achieve this goal, the ventilator must be able to compensate for both the compliance of the breathing system and the influence of fresh gas flow on tidal volume, independent of changes in lung compliance. Modern bellows ventilators (e.g., Aestiva®, Avance®, and Aisys® from GE Healthcare, Madison, WI) utilize a flow sensor at the inspiratory limb to control the volume delivered by the ventilator. The ventilator output is controlled by the flow sensor such that the set volume is delivered to the breathing circuit independent of changes in fresh gas flow or the compliance of the system between the ventilator and the flow sensor. Piston anesthesia ventilators (e.g., Fabius GS®, Apollo® and Perseus® A500 from Draeger Medical, Telford, PA) measure the compliance of the breathing system during the pre-use checkout. The compliance measurement is then used to determine how much additional volume must be added to each breath to deliver the set volume to the patient. The influence of fresh gas on delivered volume is eliminated in the piston design by altering the configuration of the circle system and including a valve that prevents fresh gas from entering the patient circuit during mechanical inspiration. In addition, the exhaled volume measurement is corrected using the circuit compliance measurement.

Newer generation anesthesia ventilators that compensate for breathing circuit compliance and for fresh gas flow are able to deliver small tidal volumes accurately under conditions of normal and low lung compliance during volume-controlled ventilation. Anesthesiologists should be aware that long, compliant circuits reduce the efficiency of ventilator performance, and increasing the circuit compliance by extending a collapsible circuit will reduce tidal volume delivery [129]. When providing ventilation for an infant with poor lung compliance, using a fixed length circuit with smaller hoses that are less compliant will optimize the anesthesia

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ventilator performance. Also, dead space ventilation can be reduced by eliminating the Y-piece and using a low-dead space heat and moisture exchanger that contains a gas sampling port. Despite significant improvements in anesthesia ventilator technology for smaller infants, an "ICU-type" ventilator may deliver better performance in terms of intended tidal volumes and ventilating pressures in small infants with poor lung compliance. These ventilators are capable of higher working gas flows, have lower dead space, and precisely control of all ventilatory parameters through advanced microprocessor designs. Assistance from a respiratory therapist may be advised in this situation because of the lack of familiarity with this equipment for most anesthesiologists.

Operating room to ICU transition

Depending upon the type and length of procedure, the patient's age and size, and any intraoperative complications, many patients will require continued mechanical ventilatory support in the postoperative period. When transitioning from the operating room to the intensive care unit, respiratory management should continue to focus upon the maintenance of FRC. This "open lung" strategy is designed to minimize PVR, optimize left ventricular afterload, and reduce any ongoing lung injury following the same principles described earlier in this chapter. Adjustment of PEEP based on flow-volume loops and the post-operative chest radiograph are traditionally tools in used to optimize the "open lung" strategy. Many ICU ventilator models allow for the use of novel forms of ventilatory management to attain and maintain physiologic FRC.

First described in adults in 1987 [130], airway pressure release ventilation (APRV) is a form of inverse-ratio ventilation generally used during spontaneous breathing. In this form of ventilation, patients spend the majority of the mechanical respiratory cycle at the set peak pressure (P_{Hi}), allowing for continual recruitment of alveoli. Spontaneous respirations oscillate around this P_{Hi} and patient effort is supplemented by "release breaths" in which the ventilator pressure is allowed to drop to a low pressure (P_{Low}). The mode is time-cycled and designed to provide sufficient time in the exhalatory phase to allow ~70% reduction of the lung volume [131]. While the continuous air-space recruitment of this mode is attractive, data in pediatric patients are mixed. At least one randomized, controlled study required early termination due to increased mortality in patients supported with APRV [132]. Moreover, the cardio-pulmonary interactions of APRV are, to date, inadequately described in the literature.

Another common form of non-conventional, high-pressure ventilation, high-frequency oscillatory ventilation (HFOV), is used in pediatric intensive care units in patients with refractory hypoxemia. Multiple recent trials and meta-analyses have shown no significant reduction in mortality, length of stay, or duration of mechanical ventilation with the use of HFOV compared with conventional ventilation [133–135]. Accordingly, many ICU providers will opt to continue conventional ventilation and utilize high PEEP levels up to 12–14 cm H_2O to maintain alveolar recruitment rather than initiate HFOV in postoperative cardiac patients.

Application of relatively high levels of PEEP to maintain alveolar patency is especially important following cardiac surgery in infants and children. In addition to the impact of cardio-pulmonary interactions on postoperative care, developments such as pulmonary hemorrhage, pulmonary edema, and/or mechanical airway compression related to swelling of the heart and adjacent structures may all necessitate higher PEEP settings. Should lung compliance be noted to decline in the OR, or if intraoperative events predict the evolution of poor lung compliance, consideration should be given to delaying sternal closure after completion of the operative course. Leaving the chest open for 24–48 hours may reduce mechanical compression of the heart and lungs and mitigates chest wall restriction of the circulation and the respiratory system. If lung compliance is very poor following surgery, extra-corporeal membrane oxygenation (ECMO) may be considered to allow lung recovery while minimizing airway pressure and its effects on ventricular function.

Specialized problems

Hypoxic gas mixture and inspired CO_2

Infants and children with single ventricle physiology and excess pulmonary blood flow (e.g., those with hypoplastic left heart syndrome) may benefit from a ventilatory strategy designed to increase PVR and diminish pulmonary blood flow. Hypoxic gas mixtures (i.e., $FiO_2 < 0.21$) or inhaled CO_2 have been used to accomplish this. Among neonatal patients with single ventricle physiology, 3% inhaled carbon dioxide improves cerebral oxygen saturation, mean arterial pressure, and oxygen delivery when compared with 17% inspired oxygen [128, 136]. However, both of these therapies are rarely applied today because of the added difficulty and risk of safely providing stable mechanical ventilation with adequate oxygenation. Infants with elevated Qp:Qs ratios are more safely managed via agents designed to reduce systemic vascular resistance (e.g., milrinone, clevidipine, sodium nitroprusside) or through surgical reduction in Qp (i.e., partial clipping of the aortopulmonary shunt).

Nitric oxide

Nitric oxide (iNO) is an endothelium-derived smooth muscle relaxant that has been used in neonates with persistent pulmonary hypertension [137, 138] and in infants and children with pulmonary hypertension related to congenital heart disease [139, 140]. iNO has also been used in adult and pediatric patients with severe hypoxemic respiratory failure due to acute lung injury [141–145]. Inhaled NO selectively reduces PVR and may decrease intrapulmonary shunting. As a result, oxygenation is improved in patients with acute lung injury due to increased perfusion of relatively well-ventilated lung units and resultant improvement in V/Q matching. Pulmonary vascular resistance and oxygenation are improved to a similar extent by doses between 10 and 60 ppm in children with acute lung injury [146]. In one study, infants with pulmonary hypertension after cardiac surgery had a decrease in pulmonary artery pressures and a 30% increase in oxygenation from the use of as little as 3 to 5 ppm of iNO with no further benefit from increasing iNO to as high as 80 ppm [147]. However, other studies have failed to show sustained improvements in PVR, oxygenation, or

outcome with the use of iNO [148, 149]. Despite a lack of high quality evidence demonstrating outcome improvements, iNO has become a mainstay of intraoperative and postoperative therapy in congenital heart disease, particularly in two-ventricle patients with known pulmonary hypertension receiving chronic vasodilators, single ventricle patients with increased PVR, those with left ventricular assist devices, who often have elevated PVR, and cardiac transplant patients with elevated PVR [150–153].

Tracheostomy in congenital heart disease

Upper and lower airway anomalies are common in infants and children with CHD. Chronic lung disease occurs in premature infants with CHD a well as those with long-standing pulmonary edema, and may result in the need for prolonged mechanical ventilation following cardiac surgery. Tracheomalacia due to vascular rings often require months to improve after reparative surgery. CHD patients may suffer perioperative neurological insults and require long term mechanical ventilation for airway protection or due to airway obstruction. In these patients tracheostomy may provide a stable airway, allow for a reduction in the need for sedation, and improve the ability for infants and children to move and interact with their surroundings. This, in turn, can lead to better physical rehabilitation, more beneficial neurodevelopmental interventions, and better facilitation of discharge to chronic care units or to home. Criteria for tracheostomy vary between institutions and generally are more conservative than for adult indications. However, mechanical ventilation for greater than 30 days and/or failure of multiple ventilation weaning attempts, with limited prospects for improvement in the near future, are common indications.

An analysis of the Society of Thoracic Surgeons' Database cases from 2000 to 2014 found that of 211,408 cardiac operations, 648 (0.31%) underwent postoperative tracheostomy [154]. The median age at tracheostomy was 2.5 months, and prematurity (26%), genetic abnormalities (46%), and preoperative mechanical ventilation (43%) were common risk factors. Postoperative adverse events after the cardiac operation were also commonly associated factors, including cardiac arrest in 20%, the use of ECMO in 13%, phrenic or laryngeal nerve injury in 18%, and neurological injury in 8%. Postoperative cardiac mortality in patients with tracheostomy was 25%. The incidence of tracheostomy increased from 0.11% in early years of the study to a peak of 0.76% in 2012. The primary diagnosis and surgical procedures in patients undergoing tracheostomy are displayed in Table 23.8. Higher volume centers (>350 cardiac surgeries annually) had a 50% lower postoperative tracheostomy rate than lower volume centers (0.34% vs. 0.61%). In a Pediatric Health Information System Database study of 5,721 hypoplastic left heart syndrome patients, 2.2% underwent postoperative tracheostomy [155]. In a separate study of the same database, 2.8% of orthotopic heart transplant patients underwent postoperative tracheostomy [156]. Tracheostomy was not associated with an increased incidence of mediastinitis.

Table 23.8 Most common primary diagnoses and procedures for patients requiring tracheostomy after operation for congenital heart disease, January 2010 to June 2014

Diagnoses and procedures	n (%)[a]	Mortality, n (%)[b]
Primary diagnosis		
Hypoplastic left heart syndrome	62 (9.6)	25 (44)
Other single-ventricle lesions	50 (7.7)	13 (26)
Atrioventricular septal defect, complete	44 (6.8)	8 (19)
Ventricular septal defect, type 2	29 (4.5)	2 (7)
Patent ductus arteriosus	25 (3.9)	6 (24)
Pulmonary atresia, ventricular septal defect	20 (3.1)	6 (32)
Tetralogy of Fallot, absence of pulmonary valve	20 (3.1)	6 (33)
Truncus arteriosus	19 (2.9)	3 (17)
Coarctation of aorta	17 (2.6)	1 (7)
Tetralogy of Fallot	14 (2.2)	2 (14)
Primary procedure		
Norwood procedure	47 (7.3)	15 (33)
Pulmonary artery banding	33 (5.1)	7 (23)
Atrial septal defect creation/enlargement	30 (4.6)	5 (17)
Ventricular septal defect repair, patch	30 (4.6)	9 (32)
Atrioventricular septal defect repair, complete	29 (4.5)	4 (14)
Patent ductus arteriosus closure, surgical	25 (3.9)	5 (21)
Aortic arch repair	21 (3.2)	3 (16)
Transplantation, heart	20 (3.1)	4 (22)
Modified Blalock-Taussig shunt	19 (2.9)	4 (24)
Pulmonary atresia, reconstruction	17 (2.6)	3 (18)

[a] Data are represented as absolute counts with percentages of total patients in study, $N = 648$.

[b] Data are represented as absolute counts with percentages of patients with each underlying diagnosis or primary procedure.

Placement of tracheostomy tubes

Tracheostomy tube (TT) designs have advanced significantly in recent years, and there are many varieties of TT that feature cuffs that can be air filled or water-filled and can be custom-made based on the patient's unique anatomy, i.e., long-segment tracheal stenosis. Multidisciplinary preoperative planning with the otolaryngology and ICU teams is important to ensure that the anesthesiologist is familiar with the TT being placed. Standard surgical and ICU protocols for TT placement include the type of incision and "stay" sutures as well as plans for postoperative sedation and first tracheostomy change by otolaryngology team; reduced variation in post-TT care promotes risk reduction during the postoperative course [157]. The operative plan needs to be well understood and communicated before the surgery. The surgical and anesthesia team should discuss plans for electrocautery - lower inspired oxygen concentrations reduce the risk of intraoperative airway fire. Important aspects of anesthetic care during TT placement also include management of the large air leak that will occur when the trachea is incised. Meticulous attention to withdrawal of the indwelling ETT to prevent inadvertent extubation during insertion of the TT is

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important. Other potential complications that may occur during TT placement include pulmonary overcirculation due to use of a high FiO_2 as well as the risk of a pulmonary hypertension crisis due to inadequate ventilation and/or light anesthesia. Rapid confirmation of correct TT placement in the trachea with capnography, lung auscultation, and the measurement of adequate tidal volumes are crucial. When transferring the patient to the ICU, the plans for managing the airway should the TT become dislodged should be clearly communicated.

Cardiac surgery in patients with pre-existing tracheostomy

Use of a TT during cardiac surgery with median sternotomy presents incremental risk due to lack of access to the airway for suctioning and TT replacement in the event that the TT becomes dislodged. In addition, airway secretions from the TT site may contaminate the chest. In most cases, after induction of anesthesia, the patient's trachea is intubated from above via the oral or nasal route. The TT is carefully removed as the trans-laryngeal ETT is advanced. The tracheal stoma must be completely sealed. An otolaryngologic surgeon can assist with packing the stoma with petrolatum or iodoform gauze and suturing the stoma closed in some cases. A clear adhesive dressing is then placed to prevent any air leak. Plans are made to replace the TT, usually at bedside in the ICU, several days after surgery by the otolaryngology team.

Summary

Neonates, infants, and children with CHD present numerous challenges to the anesthesiologist. These patients commonly have increased myocardial oxygen consumption (e.g., left-to-right shunts, valvar stenosis) and/or decreased myocardial oxygen supply (e.g., cyanosis). CPB has adverse effects on heart and lung function. Less than optimal airway management, oxygenation and/or ventilation can lead to further impairment of oxygen delivery to the heart and other organs with associated injury or death. Patients undergoing thoracic surgery may require single lung ventilation in order to optimize surgical conditions. Accordingly, the pediatric cardiovascular anesthesiologist must have advanced knowledge and expertise in managing the airway and ventilation during cardiothoracic surgery.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

27 Foz C, Peyton J, Staffa SJ, et al. Airway abnormalities in patients with congenital heart disease: incidence and associated factors. J Cardiothorac Vasc Anesth 2021;35:139–44. A comprehensive single center review of all airway anomalies, both congenital and acquired, along with risk factors for airway anomalies, and incidence of difficult intubation.

30 Hsu G, Fiadjoe JE. The pediatric difficult airway: updates and innovations. Anesthesiol Clin 2020;38:459–75. A contemporary review of progress in the approach to the difficult pediatric airway, with excellent illustrations. Video-laryngoscopy is emphasized as a newer technique with high success even in small infants.

34 Garcia-Marcinkiewicz AG, Kovatsis PG, Hunyady AI, et al. First-attempt success rate of video laryngoscopy in small infants (VISI): a multicentre, randomised controlled trial. Lancet 2020;396:1905–13. A randomized controlled trial reporting that first attempt success is significantly higher with a videolarygoscope technique, than standard direct laryngoscopy, in infants with normal airways.

36 Burjek NE, Nishisaki A, Fiadjoe JE, et al. Video-laryngoscopy versus fiber-optic intubation through a supraglottic airway in children with a difficult airway: an analysis from the multicenter pediatric difficult intubation registry. Anesthesiology 2017;127:432–40. A registry review of fiberoptic guided tracheal intubation performed through a supraglottic airway device. This technique was reported to have higher first attempt success rate than video-laryngoscopy (54% vs. 36%, $p = 0.042$) in infants less than 1 year of age with difficult intubations; with no difference at older ages.

61 Hammer GB, Manos SJ, Smith BM. Single-lung ventilation in pediatric patients. Anesthesiology 1996;84:1503–6. The classic paper laying out a systematic approach to one-lung ventilation in children of all sizes, utilizing all techniques available at the time.

82 Templeton TW, Piccioni F, Chatterjee D. An update on one-lung ventilation in children. Anesth Analg 2021;132:1389–99. An excellent updated review of new techniques of achieving one-lung ventilation, especially in small children <2 years of age, with excellent illustrations and summary tables.

95 Stayer SA, Diaz LK, East DL, et al. Changes in respiratory mechanics among infants undergoing heart surgery. Anesth Analg 2004;98: 49–55. A study of respiratory mechanics in 106 infants undergoing cardiac surgery with bypass; finding that total respiratory resistance decreased in infants undergoing corrective surgery for lesions that increased pulmonary blood flow, and was most pronounced in neonates. Among infants with normal or reduced pulmonary blood flow preoperatively, total dynamic compliance decreased after surgery.

119 Shekerdemian LS, Bush A, Shore DF, et.al. Cardiopulmonary interactions after Fontan operations: augmentation of cardiac output using negative pressure ventilation. Circulation 1997;96(11):3934–42. An important study demonstrating that negative pressure ventilation produces a significant improvement in stroke volume and pulmonary blood flow over that of conventional positive pressure ventilation.

145 Roberts JD, Polaner DM, Lang P, Zapol WM. (1992) Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:818–9. The classic paper laying the groundwork for the approval of inhaled nitric oxide for persistent pulmonary hypertension of the neonate; and its subsequent in children with congenital heart disease, and pulmonary hypertension.

164 Fuller C, Wineland AM, Richter GT. Update on pediatric tracheostomy: indications, technique, education, and decannulation. Curr Otorhinolaryngol Rep 2021;9:1–12. Online ahead of print. A well-referenced contemporary review of standardized approaches to tracheostomy in children.

CHAPTER 24

Early Tracheal Extubation, Enhanced Recovery After Pediatric Cardiac Surgery, Regional Anesthesia and Postoperative Pain Management

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Introduction

Today's medical environment is marked by financial constraints. There is increasing pressure to optimize not only medical care but also resource utilization. This notion has also affected the way we approach the treatment of children requiring surgery for congenital heart disease (CHD). For example, reducing intensive care unit (ICU) and hospital length of stay (LOS) without compromising patient's safety translates into much-needed cost savings.

Although the overarching goal of providing efficient and safe care has not changed, not only the terminology but also the approach to achieving this goal has seen a significant evolution. The following chapter will focus on perioperative management, including early tracheal extubation, adequate postoperative pain control, rapid mobilization, and hospital discharge.

Background and history

The focus on not only improving surgical techniques but also on providing efficient care to patients undergoing cardiac surgery was introduced in the mid-1980s. Diagnosis-related groups were implemented nationally into Medicare reimbursement in the United States in 1983. To slow down the rapidly increasing costs of providing medical care, this reimbursement model incentivized efficient resource use, and a shorter length of ICU and hospital stay was suddenly linked to financial benefits for the hospitals. At the same time, in congenital heart surgery (CHS), extubation at the end of the surgical procedure was almost a necessity, as reliable mechanical ventilators and sedatives with minimal side-effects for small patients were not widely available.

In 1980, Barash et al. published their experience with *early extubation* in 197 patients aged less than 3 years including neonates; of them, 61% were successfully extubated in the operating room (OR) [1]. The authors noted that "in this era of cost containment, any technique that allows maximal use of resources without jeopardizing patient safety is welcome." The concept of the day of admission surgery, early-extubation, -mobilization, and -hospital discharge became popular and eventually routine practice in adults undergoing cardiac surgery in the late 1990s. This was especially true when crowded ICUs slowed the expansion of cardiac surgery programs attempting to gain a share of the increasing number of coronary revascularizations being performed [2]. In 1994, Engelman

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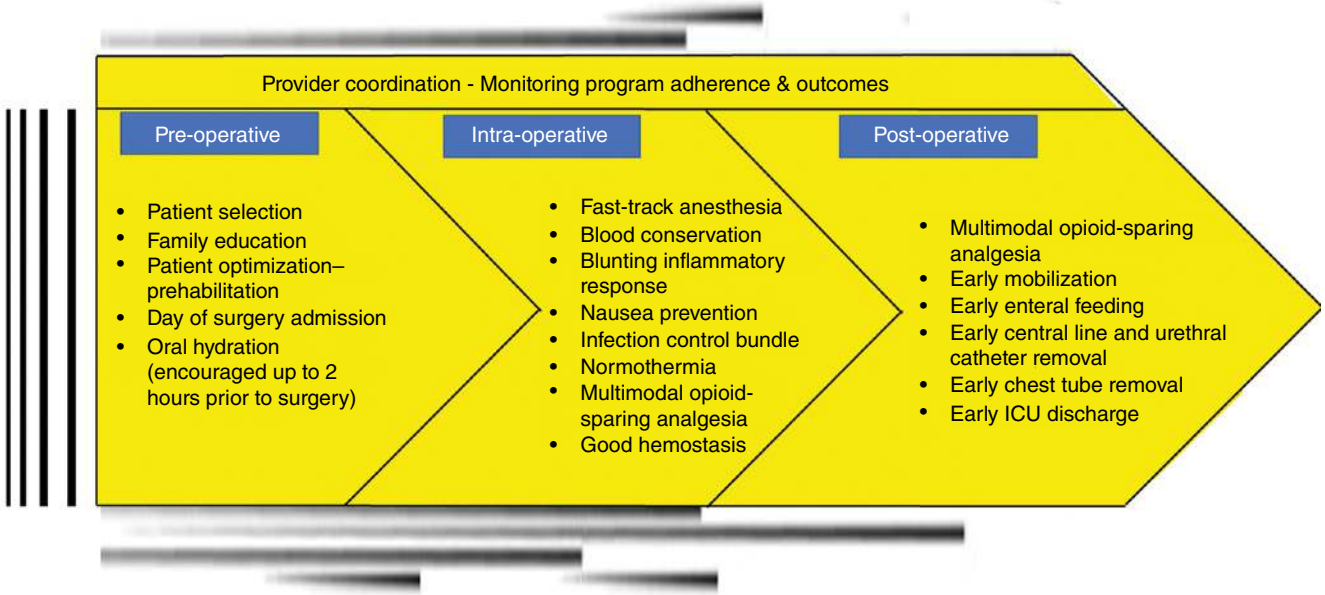


Figure 24.1 Enhanced recovery after pediatric cardiac surgery pathway.

et al. first coined the term "fast-track" in their paper, describing a complete care plan for patients undergoing cardiac surgery, which was associated with reduced hospital LOS [3].

In the field of CHS, surgical techniques developed rapidly and palliation and repair of CHD in even younger and previously inoperable children became feasible. Reports about favorable effects of high-dose opioid-based anesthesia emerged in the early 1990s, promising to reduce stress response, morbidity, and mortality [4, 5]. Administering high doses of opioids subsequently became the standard anesthetic technique in children undergoing increasingly complex CHS. This opioid-based anesthetic technique, however, necessitated prolonged postoperative mechanical ventilation (MV), and early tracheal extubation was no longer an option. Subsequently, shorter-acting drugs and anesthetic agents with less pronounced hemodynamic effects were introduced and the benefit and need of a high-dose opioid-based anesthetic were challenged [6, 7]. More recently, bundled care payment models have been implemented for specific procedures, and healthcare providers are once more encouraged to efficiently manage costs. At the same time, not meeting quality of care measures is linked to financial penalties.

Many of these past and recent changes have led hospital administrators, as well as individual healthcare providers, to re-think and investigate established, yet often inefficient, patient management strategies.

Enhanced recovery after pediatric cardiac surgery

In line with these efforts, the term "enhanced recovery after surgery" or ERAS, originally coined by Henrik Kehlet for colorectal surgery in 1997 [8], was adopted by many surgical specialties, including cardiac and pediatric cardiac surgery [9]. This patient management strategy, paraphrased by the acronym ERACS (enhanced recovery after cardiac surgery), focuses on a patient-centered, evidence-based, multidisciplinary approach to cardiac, including pediatric cardiac, surgery. ERACS strategy includes many if not most of the elements of fast-tracking children and adults undergoing surgery for CHD, that is, multidisciplinary approach, day of admission surgery, normothermia at the end of the procedure, multimodal pain management strategy, early -extubation, -mobilization, -enteral feeding, -ICU and –hospital discharge (Figure 24.1). The goals are also very similar, i.e., providing efficient, patient-centered patient care, that would help accelerate functional recovery and minimize surgical stress, thereby reducing the LOS, improving patient outcomes, optimizing resource use, and reducing associated costs. It further emphasizes routine monitoring and reporting of quality metrics and patient outcomes, aimed at continuously improving the operational aspects of this approach. The American Association for Thoracic Surgery published a consensus document on enhanced recovery after pediatric cardiac surgery [10]. Key strategies that were identified for successfully implementing and maintaining an ERACS pathway include a multi-disciplinary approach, appropriate patient selection, staff and patient/family education, protocol- and guideline-driven practice. The task force concluded that ERACS does not increase morbidity and mortality after pediatric cardiac surgery. Patient and family satisfaction with perioperative care may be improved. Roy and colleagues described their initial experience after introducing ERACS to their CHS program [11]. Compared to a matched historical control group, ERACS implementation resulted in a slightly reduced time on mechanical ventilation and LOS in ICU, although, no difference in hospital LOS was noted.

Feasibility of fast-tracking in congenital heart surgery

The multidisciplinary approach behind fast-tracking CHS patients typically includes an anesthetic technique that facilitates early tracheal extubation. Early extubation is not

consistently defined, and the term is frequently used when the endotracheal tube is removed within 6 hours after surgery [12, 13], but spans from immediate extubation in the OR up to 24 hours after surgery [10].

The feasibility and safety of extubating children immediately or soon after complex CHS had already been demonstrated in the early days of CHS, mostly out of necessity [1]. Schuller et al. reported their experience with early extubation in 1984 [14]. In 209 consecutive children undergoing complex open-heart surgery, 88% of those older than 12 months were extubated in the OR. In the same year, Heard et al. published an article on early extubation following CHS in 220 patients; of whom 147 (67%) were extubated in the OR or within 6 hours of entering the ICU [15]. None of the patients required reintubation. This was accomplished even though many of the anesthetic agents used at that time are obsolete in today's practice.

Despite the increasing popularity of a high-opioid anesthetic technique following these early reports, individual centers continued to pursue an early extubation strategy. The published reports and the recent changes in healthcare practice including ERAS pathways encouraged many institutions to adopt fast-tracking for at least some of their patients. At the time of this writing, the feasibility of fast-tracking including early extubation in children undergoing CHS has been demonstrated for most patients undergoing CHS. This includes neonates and young children [16, 17], complex surgeries [18, 19], children with single-ventricle physiology [20, 21], patients with significant co-morbidities, [22] and even in pediatric heart transplantation [23]. In a recent multicenter international survey spanning 144 pediatric cardiac surgery centers in 29 countries, extubation in the OR at the conclusion of surgery was practiced by 76% of the responding anesthesiologists, mostly for lower surgical risk procedures [24]. Table 24.1 summarizes the current literature on the feasibility of fast-tracking and early extubation in pediatric patients undergoing CHS.

KEY POINTS: FEASIBILITY OF FAST-TRACKING IN CHS

- Fast-tracking is a multidisciplinary patient management strategy aiming for efficient resource use.
- Early extubation is part of fast-tracking and is typically defined as removal of the endotracheal tube within 6 hours of surgery.
- The feasibility of fast-tracking has been shown historically out of necessity and in contemporary patient cohorts.
- Inclusion/exclusion criteria vary significantly between different centers.

Patient selection

When it comes to planning fast-tracking including early extubation for a specific patient or case, it seems prudent to understand the current evidence and have some guidance regarding who is a good candidate for such an approach. Some preoperative factors are almost universally viewed as contraindications for early extubation after CHS. For example, very few patients who have an endotracheal tube in place before the procedure will be good candidates for such a strategy. However, in many institutions, this practice is further limited to selected patients and is based on the anesthesiologist's or surgeon's preferences. While some centers consider early extubation only above a certain age and for simple procedures, others expand such a strategy to the majority of their patients. In many, if not all, of the published reports, specific exclusion criteria were applied, and it is not clear if patients who were not included could have been extubated early as well. As a matter of fact, there are reports showing successful early extubation in even the most complex procedures. Therefore, when interpreting study findings, it is important to notice not only the study design, inclusion and exclusion criteria, but also if extubation was attempted or deferred. A simple association between perioperative parameters and early extubation alone, without the specifics of extubation attempt, will not yield reliable data beyond individual practice or preferences.

The most consistent findings associated with deferred extubation are higher procedure complexity, younger age, longer aortic cross-clamp and cardiopulmonary bypass (CPB) times, and high-dose inotrope use [30, 35–42]. This has also been confirmed by prospective studies. Kin et al. found higher procedure complexity classified with the risk adjustment for congenital heart surgery (RACHS) score [43], surgery involving aortic cross-clamping, young age, and trisomy 21 to be independent predictors of the decision to not attempt extubation at the end of the procedure [32]. Very few patients in that series failed extubation once attempted. At first glance, these findings seem to classify selection criteria in a very simplified scheme. All listed factors are known preoperatively, and the findings seem to indicate that intraoperative factors such as bleeding, cardiac dysfunction requiring high inotropic support, generalized edema, etc., many of which are frequently encountered, are not significantly contributing to predicting early extubation. However, procedure complexity seems to capture many of these factors. Complex surgeries are frequently associated with longer aortic cross-clamp and CPB times, more pronounced inflammatory response, and associated findings such as a higher incidence of bleeding, generalized edema, and higher inotropic requirements, which prohibit early removal of the endotracheal tube all by themselves [29, 44, 45]. In a prospective observational study, Garg et al. [34] collected information on OR extubation and reasons for deferring extubation to a later time point in 1,000 pediatric patients undergoing surgery for CHD within an 8-month time period. Overall, 87.1% of patients were extubated in the OR, resulting in significantly shorter ICU LOS compared to a historical control group. Factors associated with deferred extubation included poor oxygenation, open sternum, ongoing bleeding, high inotrope use, and other reasons necessitating further observation in the ICU.

Aside from complex procedures, young age is one of the most frequently listed reasons for not considering early extubation [32]. In retrospective analyses, young age is consistently associated with not being fast-tracked. Davis et al., for example, assessed factors associated with early extubation following CHS. Children older than 6 months were much more likely to be extubated early compared with younger patients [29]. Winch et al. [46] found that

Table 24.1 Publications on fast-tracking in children undergoing congenital heart surgery

Reference	Study type	Patients enrolled	RACHS category	Findings
Barash et al. [1]	R	197	1–3	• 61% extubated in OR, 11% shortly after ICU arrival, 4% reintubation • Longer CPB time associated with not extubating • Fewer pulmonary complications in early extubation group
Schuller et al. [14]	R	209	1–5	• 80% extubated in OR, 2.4% reintubation • Younger age, PAH, and severe preoperative heart failure, associated with not extubating in OR
Heard et al. [15]	R	220 (1 day–16 years)	1–3	• 67% extubated in OR or within 6 hours after ICU arrival, no reintubation • Fewer pulmonary complications with early extubation • Longer CPB time associated with prolonged MV
Laussen et al. [25]	R	102	1 (ASD only)	• 38% extubated in OR • OR extubation safe • Shorter hospital LOS, and lower costs associated with early extubation
Heinle et al. [17]	R	56 (<90 days)	1–6	• 50% extubated in OR or within 3 hours in ICU • 3 patients required reintubation • Patients extubated early had shorter ICU/hospital LOS, reduced costs
Vricella et al. [26]	R	201	1–3	• 87% extubated in OR, 94% within 4 hours after surgery, 2.6% required reintubation • Fast-tracking in surgery for CHD is feasible and safe
Lofland [27]	P/O	50	3 (bi–Glenn, Fontan only)	• All patients extubated either in OR or within 1 hour postoperatively • Pain-free spontaneous ventilation resulted in superior hemodynamics
Neirotti et al. [19]	R	901	1–3	• 73% extubated in OR, 2.5% reintubation • Younger age, lower weight were risk factors for deferring OR extubation • Simplified postoperative care and increased patient and family satisfaction
Kloth and Baum [28]	R	102 (>2 months)	1–6	• 47% extubated in OR or on ICU arrival, no reintubation • Only RACHS 1–3 extubated early • Mild respiratory acidosis immediately following early extubation well tolerated • Young age, low weight, long CPB time, DHCA, high inotrope use, PAH, are among the factors why extubation was not attempted
Davis et al. [29]	R	219 (≤36 months)	1–6	• 47% extubated within 24 hours • Age >6 months, no PAH, no CHF, gestational age >36 weeks, associated with early extubation • Intraoperative factors less important, except for the cross-clamp time
Vida et al. [22]	R	100 (median age 2.5 years)	2 (VSD + PAH only)	• 65% extubated in OR, overall 90% extubated within 6 hours after surgery, two patients extubated early required reintubation • Trisomy 21 and longer CPB time are risk factors for postoperative complications and prolonged MV • PAH is not a contraindication for early extubation • Degree of PAH not associated with the incidence of postoperative complications, ICU and hospital LOS • Decreased ICU and hospital stay, reduced costs, lower in-hospital mortality with early extubation

(*Continued*)

Table 24.1 (Continued)

Reference	Study type	Patients enrolled	RACHS category	Findings
Mittnacht et al. [30]	R	224 (>1 month, <18 years)	1–4	• 79% in OR, no reintubation for respiratory reasons • Younger age, longer CPB time, and high inotrope use associated with not extubating in OR
Morales et al. [21]	R	112	3 (Fontan only)	• 34% extubated in OR, no reintubation • Lower inotrope use, shorter ICU and hospital LOS, and decreased costs with early extubation
Preisman et al. [31]	P/R/O	50 (OR extubation)/50 (control)	1–3	• No difference in mortality, morbidity, reintubation • Shorter ICU and hospital LOS in OR extubation group
Kin et al. [32]	P/O	Site 1: 275 (2 weeks–18 years, median 18 months) Site 2: 49 (median 25 months)	1–3	• Site 1:89% extubated in OR (three patients required reintubation for respiratory reasons) • Site 2: 65% extubated in OR (no reintubation) • All patients with cross-clamp and RACHS-1 extubated in OR • RACHS, trisomy 21, age, independent predictors of OR extubation
Hamilton et al. [33]	R	50 (OR extubation)/50 (control)	1–3	• Lower inotrope use, and shorter hospital LOS in early extubation (OR) group • More reintubations in early extubation but statistically not significant
Garg et al. [34]	P/O	1,000 (1 day–18 years)		87% extubated in OR, shorter ICU stay, and lower resource use
Harris et al. [35]	R	613, including neonates		71% extubated in OR, 89% within 24 hours including neonates
Varghese et al. [18]	R	148, neonates		30.4% extubated in OR,
Varghese et al. [20]	R	23, stage 1 palliation		5 patients extubated in OR, no difference in outcomes
Shinkawa et al. [36]	R	909, including neonates		64.9% extubated in OR, decreased ICU LOS and costs, no difference in reintubation rate, longer OR turnover
Fukunishi et al. [37]	R	359 (1 month–18 years)		83% extubated in OR, lower RACHS-1 score resulted in higher extubation rate
Wu et al. [38]	R	2,060 (<18 years)		65% extubated in OR, 16.1% within 6 hours, reintubation rate 2.0%

R, retrospective; P, prospective; O, observational; ICU, intensive care unit; OR, operating room; RACHS, Risk Adjusted Congenital Heart Surgery Score; LOS, length of stay; CPB, cardiopulmonary bypass; PAH, pulmonary arterial hypertension; MV, mechanical ventilation.

children younger than 3 months were less likely to be extubated early. However, extubation practice varies significantly and even neonates have been extubated successfully immediately after CHS [17]. Age also needs to be assessed in the context of the planned procedure. Certain more complex procedures may be performed later in life, while a simple procedure in an infant may pose a much smaller risk for not qualifying for early extubation. The fact that age alone is not a good selection criterion for fast-tracking is also supported by the published literature. Kin et al. [32], for example, found that the relationship between age and attempted OR extubation was inconsistent and not linear. Beyond the age of 2 years, however, age did not impact the likelihood of OR extubation. Similarly, in Garg's study [34] representing a large number of patients and a high overall extubation rate (87.1%), OR extubation was accomplished in 40% of neonates, 69.7% of 1–3-month-olds, 85.5% of 3 months–1-year-olds, and leveled off thereafter. In general, these data indicate that successful extubation in the OR can be accomplished more reliably in children older

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than 2–3 months of age. Younger infants and neonates need not be excluded from such a strategy; however, the incidence of encountering contraindications to early extubation at the end of the procedure or soon after in the ICU is typically much higher at this very young age.

Chromosomal abnormalities also account for patients not being considered for early extubation. While not a contraindication *per se*, patients with a genetic variation known to be associated with difficult airway instrumentation, or an increased risk of airway obstruction (e.g., trisomy 21), must be evaluated carefully before attempting early extubation. This is even more of a concern following a long CPB time, which is frequently associated with generalized edema possibly involving the upper airway.

Pre-existing or worsening of pulmonary arterial hypertension (PAH) deserves particular attention. Many practitioners would not attempt early extubation in patients with pre-existing PAH. However, this practice has been challenged, and there are reports of successful extubation following CHS even in patients with significant PAH [22]. In a retrospective analysis of factors associated with early extubation, PAH was not found to be an independent predictor of OR extubation [30], and preoperative PAH did not predict patients who were not extubated in the OR in a similar prospective study [32]. In the latter study, however, significant PAH following CPB was the most common reason for deferring extubation at the end of the procedure. While there is no question why PAH increases the risk for many adverse perioperative events [47–50], it is important to recognize that merely using the current definition of PAH (right-sided pressures ≥20 mmHg) [51] does not accurately reflect such risks in children with CHD [52]. It is often difficult to predict the degree of PAH following surgical repair and, even more importantly, right ventricular failure merely by preoperative right-sided pressures. Assessment of pulmonary vascular resistance (PVR), reactivity to pulmonary vasodilators, as well as the relationship between right-sided pressures and systemic arterial pressure is typically included in the evaluation of PAH in children undergoing CHS [53]. Following weaning off CPB, patients can be reassessed, and even in the setting of pre-existing PAH, patients can often be extubated as long as the right ventricular function is adequate, and no inhalational pulmonary vasodilators are required.

The likelihood of early extubation following CHS can be better predicted by combining several of the risk factors. Kin et al. developed a risk score model based on factors found to be independently associated with extubation in the OR following surgery [32]. All patients undergoing CPB surgery without aortic cross-clamp and simple procedures (RACHS 1, for example, secundum atrial septal defect) were extubated in the OR. Higher RACHS scores and the addition of trisomy 21 as an additional risk factor increased the chance of deferring extubation. Similarly, Davis et al. found age <6 months, prematurity, congestive heart failure, and pulmonary hypertension to be associated with the chance of failing extubation within 24 hours after surgery. Adding individual factors increased the chance of failing early extubation [29]. Factors associated with early extubation in individual studies can be found in Table 24.1.

Implementation and maintaining fast-tracking

The cumulative experience of fast-tracking patients undergoing pediatric cardiac surgery clearly highlights the multi-disciplinary approach required for the successful implementation of such a strategy. Many institutions where fast-tracking has been practiced successfully have started with low complexity cases and older children, and eventually adopted this approach to a broader patient population [54]. With the rebranding of fast-tracking and adoption of ERACS protocols, more data will likely emerge on implementing and maintaining this strategy in pediatric cardiac surgery also. Roy et al. [11] described their initial experience with introducing an enhanced recovery after CHS program at their institution. Key elements for implementation included an initial assessment of the evidence based ERACS interventions in pediatric CHS, multidisciplinary consensus building and development of institutional ERACS guidelines, as well as monthly sharing of outcome data for continuous process improvement. Despite this, the authors comment on the suboptimal adherence to ERACS guidelines.

The Pediatric Heart Network Collaborative Learning Study used collaborative learning principles to implement early extubation guidelines across four active study sites and five control sites [55]. Overall compliance with early extubation guideline adoption was high. An increase in early extubation rates, from 11.7% before to 66.9% after guideline implementation, were seen for patients undergoing tetralogy of Fallot (TOF) repair. No change was noted for coarctation of aorta repair. There was no increase in the reintubation rate during the study period. Although all active sites reported a significant decrease in time to extubation, significant variability between sites was noted (i.e., magnitude of change: –73.3% to –99.2%) [56]. Following this initial rollout, the investigators assessed if this initiative also impacted extubation practice in patients not targeted in the initial trial; "spillover" [57]. One year after the initial practice guideline was implemented, one of the four active study sites also noted a significantly higher extubation rate in patients undergoing ventricular septal defect repair. No change was seen in patients undergoing higher complexity surgeries. The same group of investigators also looked at the sustainability of the observed change in early extubation rate in patients undergoing TOF [58]. One year after initial study completion, the early extubation rate declined from 67% to 30%, and the median time to first extubation attempt increased from 4.5 to 13.5 hours. Only one out of four hospitals maintained the extubation rate achieved during the initial study. Sustaining and even expanding an early extubation practice, without doubt, require continuous work from all stakeholders involved, including transparency and reporting of outcomes and resource use.

KEY POINTS: PATIENT SELECTION FOR EARLY EXTUBATION

- Preoperative factors can be used to help stratify patients who are good candidates for early extubation.

- Many of the traditionally taught "contraindications" for early extubation have been successfully challenged.
- The ultimate decision to extubate can only be made after the surgical procedure if extubation criteria are fulfilled.

Anesthesia technique

Although certain predictors can help select patients who are good candidates for early extubation even preoperatively, the ultimate decision to attempt extubation will always be deferred to the end of the procedure or ICU. For the purpose of fast-tracking and, in particular, early extubation, an ideal anesthetic would allow early extubation and at the same time provide stable hemodynamics, adequate analgesia, and sufficient blunting of the stress response. In the early days of CHS, the use of potent inhalational anesthetics allowed for early extubation at the end of, or within a few hours after surgery. However, a mainly inhalational anesthetic-based technique is not always tolerated and can be associated with significant side effects at higher concentrations. An opioid-based anesthetic provides stable hemodynamics and superior suppression of stress response, but typically requires prolonged MV. The addition of a neuraxial anesthetic is advocated by some practitioners and will be discussed in more detail later in this chapter. There are concerns, however, about adequate evidence regarding the safety of a neuraxial technique in the cardiac surgery setting.

Made possible in large part by the introduction of improved and new anesthetic agents such as modern inhalational anesthetics, short-acting opioids, hypnotics, and sedatives with favorable pharmacodynamics and pharmacokinetic profiles, all the above-mentioned goals can be accomplished, and the side-effects of each individual technique minimized. Such a balanced anesthetic consisting of an inhalation-based technique supplemented with a short-acting opioid is the basis of most of the modern anesthetic techniques aiming for fast-tracking CHS patients and will be discussed in more detail here.

Patients who qualify for fast-tracking are often admitted on the day of surgery, and frequently intravenous (IV) access has not yet been established. Therefore, an inhalational induction technique with sevoflurane is typically chosen for induction and is well tolerated in most patients. If true contraindications to an inhalational induction technique apply, IV access should be established, and ketamine or etomidate can be used as induction agents. With a true inhalation-based fast-tracking technique, the inhalational agent is administered throughout the case, including on CPB. The CPB machine must therefore be equipped with a vaporizer. Alternatively, a continuous infusion of IV agents with hypnotic properties can be used during CPB. As a short-acting hypnotic with favorable pharmacokinetic and pharmacodynamics properties, propofol is frequently used during CPB for patients who are fast-tracked [59]. If, however, a decrease in systemic vascular resistance (SVR) must be avoided, a high-dose opioid technique or the use of ketamine should be considered. Ketamine administered as a continuous infusion maintains stable hemodynamics in most CHS patients.

Regarding IV opioid use, shorter-acting opioids such as fentanyl are preferred. Early extubation can still be accomplished as long as the cumulative dose is limited, and larger repetitive doses avoided toward the end of the procedure. Frequently, not more than 5–10 μg/kg fentanyl is given for the whole case [25, 28, 30, 31], which is significantly less than the doses used for a high-dose opioid technique. Remifentanil is an ultra-short-acting opioid that is metabolized by non-specific esterases in plasma and tissues and minimally affected by CPB [60]. The use of remifentanil allows conduction of a high-dose opioid anesthetic with the benefits of reducing stress response, but with a fast recovery facilitating early extubation [61–63]. The challenge is to provide adequate analgesia after an infusion of remifentanil is discontinued due to its rapid elimination. A neuraxial technique, non-opioid analgesics, and dexmedetomidine can be helpful for this purpose.

Dexmedetomidine is a sedative agent that confers sedation by selectively binding to central α_2 adrenoceptors. Respiratory indices and upper airway patency are maintained during dexmedetomidine sedation in children [64–67]. In addition to sedative and analgesic-sparing effects, dexmedetomidine use has also been reported to reduce stress response in patients undergoing cardiac surgery [68]. Additional favorable properties supporting dexmedetomidine's role in the fast-tracking setting are the reduced incidence of emergence delirium after inhalational anesthesia in children [69–71] and its possible role in reducing the incidence and even treatment of arrhythmias [72]. Additionally, emerging data mostly from in vitro studies show potential neuroprotective effects [73, 74]. Because of these favorable properties, dexmedetomidine is even used throughout the case by some practitioners and allows the reduction of opioid requirements for fast-tracking purposes. Undesirable hemodynamic effects of dexmedetomidine such as bradycardia, hypotension, hypertension, decrease in cardiac output [75], as well as an increase in PVR, especially with high doses or fast bolus administration, have all been described. These side effects, however, are highly dose- and age-dependent. Typically, dexmedetomidine is well tolerated in older children [76]; however, little data are available regarding safe doses in infants and particularly in neonates. There are data showing that dexmedetomidine clearance in neonates and infants is reduced [77–80], and accumulating drug levels causing bradycardic side effects may occur. In a recent pharmacokinetics and safety trial in neonates undergoing cardiac surgery, clearance was significantly reduced; however, dose adjustments resulted in a low incidence and severity of adverse events noted [81].

It must also be noted that at this point dexmedetomidine is still approved only by the US Food and Drug Administration (FDA) for use in adults for ICU sedation up to 24 hours. In clinical practice, however, dexmedetomidine has been widely used in children even for prolonged periods of time [82]. A Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review can be found on the FDA web page [83].

In a Pediatric Heart Network-sponsored multicenter Collaborative Learning Study, the change of anesthesia practice was compared before and after early extubation study guideline implementation [84]. Clinical practice guideline implementation aimed at early extubation in patients

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following repair of coarctation of the aorta or TOF was accompanied by a significant decrease in opioid and midazolam use, no change in intraoperative median volatile anesthetic use, and intraoperative dexmedetomidine administration was an independent predictor of early extubation.

In summary, fast-tracking and early extubation are facilitated by modern anesthetic agents combined with strategies to provide good analgesia without significant respiratory depression.

KEY POINTS: ANESTHESIA TECHNIQUE

- A balanced, inhalational anesthetic-based technique is usually chosen for fast-tracking.
- Opioid use is limited, and short-acting opioids are preferred.
- Non-opioid analgesics and opioid-sparing drugs such as dexmedetomidine are used to reduce opioid use.
- Neuraxial techniques can supplement pain management, but their use is controversial.
- Regional anesthesia techniques, particularly thoracic fascial plane blocks are increasingly being used to help reduce opioid use.

Surgery and CPB considerations

Surgical and CPB techniques contribute significantly to the ability to fast-track patients and have an impact on anesthetic management. Aside from the quality of the surgical repair, it is increasingly recognized that outcomes can be improved by reducing the inflammatory response [85] and limiting surgical trauma [86]. For example, avoiding or limiting prolonged periods of deep hypothermia [87] and circulatory arrest [88] reduces CPB duration and associated complications such as cardiac dysfunction, coagulopathy, and transfusion requirements [89]. Limiting the inflammatory response results in less generalized edema and improves pulmonary function [90–92], all important components to successfully fast-tracking CHS patients. Minimally invasive surgical techniques [93–95], hybrid procedures [96], or alternate surgical access for selected CHD [97] can further contribute to limiting surgical trauma.

Significant changes have also been made to CPB and perfusion techniques. These improvements often benefit patients who are considered for fast-tracking and include miniaturized CPB circuits [98–100], retrograde autologous priming [101], beating heart surgery techniques [102], less cooling [103–105], pulsatile CPB [106], and selective perfusion strategies [107]. Modified ultrafiltration (MUF) is also frequently part of a fast-tracking protocol and has been shown to decrease edema and improve pulmonary and cardiac function [108–110]. Immediate effects on hematocrit and coagulation also help fast-tracking [111]. Many of these techniques are controversial and not universally practiced, however, and the safety and possible outcome benefits are still being evaluated. Nevertheless, many of the currently ongoing changes to the practice of CHS promise to be beneficial to fast-tracking.

KEY POINTS: SURGERY AND CPB CONSIDERATIONS

- Surgical and CPB techniques contribute significantly to fast-tracking.
- Measures to reduce inflammatory response are key to the ability to fast-track.
- Selective perfusion techniques avoid prolonged periods of circulatory arrest and profound cooling.

Failed extubation and prolonged mechanical ventilation

It must be noted that selection criteria for patients who are good candidates for fast-tracking and early extubation are not necessarily the same as the factors associated with extubation success and/or prolonged MV. Selection criteria that were discussed earlier can help guide physicians in planning an anesthetic, and based on prior studies, carefully selected patients will fulfill extubation criteria in most cases. However, assessment of extubation criteria and the decision to remove the endotracheal tube can only be made at the end of the procedure or in the ICU immediately prior to the planned extubation. Extubation success is only obvious once the patient can sustain spontaneous ventilation without significant respiratory support. And if a patient fails extubation or extubation was never attempted and requires prolonged ventilatory support, certain factors have been found to be associated with prolonged MV. These considerations will be discussed in more detail here.

If early extubation was planned but not attempted, the anesthesiologist together with the surgeon will have made this decision based on subjective as well as objective observations and findings. In general, extubation criteria have been defined, are relatively consistent between practitioners, often follow specialty society guidelines and recommendations, and are not different in the CHS setting. However, the reasons for deciding to proceed with attempting extubation may vary greatly between institutions. In a prospective observational study, almost all patients presenting for CHS who did not require mechanical support preoperatively were considered as candidates for extubation at the end of the surgery [19]. The authors further assessed the factors that made the practitioners decide not to attempt extubation immediately following surgery. Significant pulmonary hypertension following CPB, hypoxemia, bleeding/coagulopathy, airway compromise (edema), insufficient respiratory effort, hypothermia, and open chest were listed by the practitioners as the main reasons for diverting from the original plan to remove the endotracheal tube at the end of the procedure. Preisman et al. listed hemodynamic instability, open chest, hypoxemia, hyperlactatemia, inadequate urine output, and higher transfusion requirements as reasons why patients were excluded from planned early extubation [31], while Kloth et al. [28] listed young age, low weight, significant co-morbidity, preoperative MV, high inotropic support, ongoing bleeding, airway concerns, significant PAH, and nitric oxide use.

Once the endotracheal tube is removed, extubation success is relatively high in most studies. Extubation failure is often defined as reintubation within 96 hours after extubation [112, 113]. Reintubation rates reported in patients following fast-track CHS do not differ from those in children who were not fast-tracked, or from any other major surgery setting, and typically do not exceed 4% in the majority of published studies [19, 21, 26, 30, 114]. A review of the literature and meta-analysis confirmed these findings, and reintubation rates did not differ between patients who were extubated early vs. late [13]. In neonates and very young infants, however, extubation failure and reintubation may be higher [17, 115]. Higher surgical risk procedures were also associated with an increased incidence of reintubation [54]. In the Pediatric Cardiac Critical Care Consortium clinical registry, extubation failure defined as reintubation less than 72 hours after the first planned extubation was found in 11% of patients, the majority (61%) within 24 hours [116]. Extubation failure ranged from 5 to 22% between various centers, and in a secondary analysis [117], the staffing model and percentage of nursing staff with critical care certification were associated with lower odds of extubation failure.

Reasons for reintubation and factors associated with failed extubation have been listed by several investigators. Harrison et al. performed a retrospective chart review and analyzed independent predictors of reintubation within 24 hours after extubation in children aged 3 years or younger undergoing CHS [45]. Reintubation was required in 22 out of 219 surgeries, and trisomy 21, surgery with deep hypothermic circulatory arrest, and pulmonary hypertension as the strongest predictor were independently associated with failed extubation. Gupta et al. [113] evaluated extubation failure in infants undergoing the Norwood operation. Pulmonary complications, cardiac dysfunction, diaphragmatic paralysis, and airway-related complications were the most common reasons why patients required reintubation. Almost identical causes of extubation failure were found in patients undergoing repair for TOF[112]. Another study evaluating extubation success following CHS found lung mechanics and associated abnormalities of respiratory function, such as increased work of breathing, as the main cause for failing extubation [118]. Other factors frequently identified as reasons why patients fail extubation are neurologic complications, cardiovascular insufficiency, inotrope score, poor oxygenation, and respiratory acidosis [119, 120]. When evaluating reintubation rates, it must be recognized that reintubation may be required for reasons other than not sustaining spontaneous ventilation. This is not a failure of an early extubation strategy *per se*. These patients would have been successfully extubated but required reintubations for other reasons, such as return to the OR for surgical intervention, sepsis, or pneumonia, and thus, in the context of fast-tracking, reported reintubation rates must be interpreted accordingly.

The decision to continue MV in patients following surgery for a few hours or until the next day is often based on institutional preferences. Prolonged MV, however, often defined as MV beyond the third postoperative day, is usually secondary to a more complicated postoperative course. A prospective observational study found factors associated with prolonged MV to be inconsistent and heterogeneous and included pulmonary hypertensive events, delayed sternal closure, peritoneal dialysis, pulmonary complications, low cardiac output syndrome, neurological events, nitric oxide use, and tracheomalacia [44]. In a retrospective study, independent risk factors of prolonged MV were surgical complexity assessed with the RACHS score, nosocomial pneumonia, low cardiac output syndrome, postoperative positive fluid balance, and extubation failure [121]. Phrenic nerve injury, pleural effusions, pulmonary hypertension, and other airway complications are typical pulmonary complications that require prolonged MV [122]. Trisomy 21 is also frequently associated with a more complicated postoperative course, including prolonged MV [123].

Box 24.1 summarizes common reasons for deferring planned extubation, early extubation failure, and prolonged MV following CHS.

Box 24.1: Common reasons for deferring early extubation, extubation failure, and prolonged mechanical ventilation in patients undergoing congenital heart surgery

Common reasons for deferring planned early extubation

- Preoperative mechanical ventilation
- Pulmonary hypertension (pre-and post-CPB)
- Pulmonary hypertension requiring nitric oxide
- Insufficient respiratory effort
- Airway compromise, generalized edema
- Hypoxemia
- Hemodynamic instability (high inotrope use, hyperlactatemia, open chest, extracorporeal membrane oxygenation (ECMO), hemodynamically significant arrhythmia)
- Ongoing coagulopathy, increased transfusion requirements
- Long CPB, aortic cross-clamp time, deep hypothermic circulatory arrest (DHCA)
- Young age, low weight
- Hypothermia
- Inadequate urine output
- Chromosomal abnormalities (e.g., trisomy 21).

Common reasons for failed early reintubation within 96 hours after extubation

- Pulmonary hypertension
- Cardiovascular instability
- Ongoing coagulopathy
- Pulmonary: insufficient respiratory effort, increased work of breathing, hypoxemia
- History of trisomy 21
- Phrenic nerve paralysis
- Pleural effusion
- Other complications requiring surgical intervention

Reasons for prolonged mechanical ventilation (>72 hours) following CHS

- Pulmonary hypertension (particularly nitric oxide use)
- Pulmonary complications, pneumonia, phrenic nerve injury, tracheomalacia
- Neurologic complications
- Hemodynamic instability, low cardiac output syndrome, low urine output requiring dialysis
- Open sternum

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; DHCA, deep hypothermic circulatory arrest.

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KEY POINTS: FAILED EXTUBATION AND PROLONGED MV

- Deferring planned extubation to a later time point is different from failed extubation.
- Extubation criteria do not differ from patients who are not fast-tracked.
- Reintubation rates in fast-tracked and conservatively managed children are comparable.
- Prolonged MV beyond the third postoperative day is unrelated to fast-tracking, and associated factors comprise a wide spectrum of complications associated with CHS.

Benefits of fast-tracking

The benefits of fast-tracking were noticed even in the early days of CHS when extubation at the end of a procedure was done more out of necessity than by choice. In 1979, Barash et al. noted fewer complications from MV, earlier patient mobilization, increased patient and parent satisfaction, and optimal resource use with possible cost benefits [1]. Further reports on early extubation in pediatric cardiac patients followed, and the increasing experience with this approach led to recognizing and reporting possible benefits in this patient population. Many of the initially reported benefits are still valid, and even though modern ventilator technology has significantly improved, avoiding prolonged periods of MV is usually preferred. Patients without MV typically require less sedation, which often leads to lower inotropic (hemodynamic) support, more rapid patient mobilization, decreased ICU and hospital LOS, and possibly decreased costs [19, 31, 33]. Aside from cost savings, a prolonged hospital stay can increase the risk of hospital-acquired complications such as infections. The risk of hospital-acquired infections cannot be underestimated and is one of the main reasons why fast-tracking has been adopted, particularly in some of the developing countries with a higher surgical wound infection rate. Additionally, early extubation allows earlier mobilization and verbal communication between the child, parents, and hospital staff involved. Consequently, patient and parent satisfaction are increased in children who are extubated in the OR, or soon after ICU arrival. A large meta-analysis on early extubation in CHS even found lower in-hospital mortality, as well as a trend toward shorter ICU and hospital LOS, lower costs, and fewer respiratory complications in patients who were extubated early; however, it is not clear if selection bias can partially explain these findings [13]. Benefits found with early extubation are listed in Table 24.1 and Box 24.2.

Certain types of CHS patients may benefit more than others from fast-tracking, and in particular from early extubation and spontaneous ventilation. In patients with single-ventricle physiology undergoing bi-directional Glenn or Fontan procedure, early extubation and spontaneous ventilation have been associated with improved hemodynamics [21, 27, 124, 125]. Other reported benefits include lower inotropic support, earlier chest tube removal, and shorter ICU LOS [126, 127]. Lower intrathoracic pressure associated with spontaneous ventilation increases central venous blood return, which becomes the driving force of pulmonary blood flow across the pulmonary vascular bed and thus for maintaining left ventricular preload and cardiac output [128, 129]. In a study of 50 patients undergoing either bidirectional Glenn or Fontan operation who were extubated either in the OR or within 1 hour postoperatively, decreased pulmonary artery pressure and increased cardiac index were recorded following extubation [27]. Morales et al. [21] found mean pulmonary artery and atrial pressure to be lower and mean arterial blood pressure to be higher in patients who were extubated soon after surgery. In patients who were extubated in the OR, less inotropic support was required, the time to chest tube removal was shorter, and ICU/hospital stay and costs were reduced. In particular, for patients who have undergone a bidirectional Glenn surgery, mild hypercapnia frequently seen following early extubation should increase blood flow to the superior vena cava (SVC) and pulmonary circulation from cerebral vasodilation [130–132]. Hoskote et al. investigated the systemic and pulmonary hemodynamic effects of different CO_2 tensions in patients following bidirectional Glenn anastomosis in a prospective trial [133]. Mild hypercarbia ($PaCO_2$ up to 55 mmHg) resulted in improved systemic oxygenation, increased systemic (Qp) and pulmonary (Qp) blood flow (Qp/Qs unchanged), increased cerebral blood flow, and decreased SVR. PVR remained unchanged in this study. In another retrospective study in children following right heart bypass surgery, early extubation and spontaneous ventilation resulted in decreased PVR, lower mean pulmonary artery pressure, and fewer pulmonary complications such as pneumonia and atelectasis [128]. Despite the findings showing that mild permissive hypercapnia may be beneficial or at least well tolerated in patients following bidirectional Glenn and Fontan procedures, there remains widespread concern and controversy about the safety of fast-tracking and early extubation in this patient population, particularly as the age of bidirectional Glenn patients continues to decrease and is often 2–3 months [134]. Kawaguchi and colleagues examined the impact of an institutional policy change on early

Box 24.2: Benefits associated with fast-tracking and early extubation

- Fewer ventilator-associated complications:
  - Accidental extubation
  - Laryngotracheal trauma
  - Mucous plugging of the endotracheal tube
  - The pulmonary hypertensive crisis from endotracheal suctioning
  - Barotrauma from positive pressure ventilation
  - Ventilator-associated pulmonary infections and atelectasis
- Reduced requirements for sedatives/analgesics
- Greater hemodynamic stability
  - Beneficial effects of spontaneous ventilation in stage 2 & 3 single-ventricle palliation
  - Lower inotrope use
- More rapid patient mobilization
  - Earlier ICU discharge
  - Decreased hospital length of stay
- Reduced costs
- Greater parent and patient satisfaction

extubation in patients undergoing Fontan palliation [135]. The policy change was associated with an impressive reduction in pediatric intensive care unit length of stay (PICU LOS) (average 4.1 days; 95% CI −1.2 to −6.9). Fluid balance did not differ, and although the rate of reintubation was statistically not different, hemodynamic instability was the main reason for reintubation prior to policy change and bleeding and respiratory etiology listed most commonly in the time period after.

Cost containment in healthcare has become more important than ever before and centers caring for children with CHD are not exempt from this. The strongest predictors of costs for patients undergoing cardiac surgery are usually intensive care and hospital LOS, OR time, and postoperative complications. Any technique resulting in earlier patient discharge without compromising patient's safety should therefore result in cost savings. While many studies on patients undergoing CHS have shown a decrease in ICU and hospital LOS, as well as cost savings from shorter time on MV [13, 17, 21, 22, 136], overall cost benefits from fast-tracking and early extubation, are not easily evaluated. Most studies reporting on cost savings acknowledge difficulties in comparing historical control groups with contemporary patient care. Results from randomized studies in adult cardiac surgery, however, clearly demonstrated cost benefits from fast-tracking patients [137–139]. Most of those studies conclude that fast-tracking results in shorter ICU and hospital LOS, and decreases in resource use, all of which led to decreased costs. While it may be difficult to compare costs between different institutions and patient populations, it is quite likely that at least some of these findings can be extended to CHS. Heinle et al. [17], for example, found significant cost reductions in patients who were extubated early due to shorter ICU/hospital LOS. Vida et al. showed that patients who were extubated early had significantly shorter ICU and hospital stays, and every additional day spent on the ICU increased overall costs of the procedure by 10% [22]. In patients undergoing atrial septal defect (ASD) repair, for example, Laussen et al. found similar ICU charges regardless of the time of extubation; however, combined ICU and OR charges were reduced mainly because of avoidance of postoperative MV [25].

Most of these reports on cost savings are based on retrospective analyses and are not from randomized, contemporary matched patient populations. When comparing costs using a historic control group, additional factors such as the experience of the surgeon, inflation, and increased costs due to new technologies must be considered and these factors are almost impossible to accurately account for. Lawrence et al. [140] compared their single-institution experience of implementing fast-tracking with outcomes from a large contemporary nationwide database for the same time periods. When fast-tracking including early extubation (the goal was to extubate at the end of the procedure in the OR) was fully implemented, the median hospital LOS at their institution decreased by 1 day compared with the earlier time period, while nationally LOS remained unchanged. This translated into significant cost savings (33 and 35% for ASD and ventricular septal defects, respectively), whereas an increase in costs was noted nationally for the repair of both congenital heart defects in the same time period. A multiple regression analysis confirmed the decrease in both LOS and costs to be significantly greater at their institution compared with the nationwide database. Hospital mortality and 2-week readmission rates remained unchanged and were not different from the national rates. This is particularly important, as an increase in postoperative complications associated with fast-tracking and early extubation would outweigh the potential cost-saving benefits. Similarly, any significant increase in turnover times in the OR could easily jeopardize cost savings.

Holowachuk et al. [141] performed a cost savings analysis after the implementation of an early extubation strategy for eight Society of Thoracic Surgeons (STS) benchmark operations at their institutions. Costs were compared to a large contemporary STS database cohort. Early extubation was associated with a mean cost savings of US$ 12,976 (range US$ 11,934–$14,059) per procedure; the majority of which were related to direct costs savings, i.e., resource utilization.

In the Pediatric Heart Network, Collaborative Learning Study, researchers also examined if the implementation of an early extubation clinical practice guideline in patients undergoing TOF and coarctation of aorta led to cost savings [142]. The change in total hospital costs adjusted for geographic region and inflation was evaluated both before and after guideline implementation and the change was compared between study and control sites. There was an overall 27% decrease in hospital costs (interquartile range, −41.5 to −13.2%) in patients undergoing TOF repair at the active sites and costs were unchanged at the control sites. Most cost savings were related to clinical services, including mechanical ventilation and respiratory services, pharmacy, and blood gas-related costs. No change in costs was noted for patients undergoing coarctation of aorta repair. Although these results are in line with prior findings, this study also highlights that conclusion about potential cost savings cannot be easily generalized across the whole spectrum of CHS, and all institutions.

Early extubation is only one element in the multidisciplinary approach to fast-tracking CHS patients. A meta-analysis of randomized, controlled trials on fast-tracking in patients undergoing coronary artery bypass grafting (CABG) showed that standardized perioperative care including an early extubation protocol and not just early extubation *per se* was essential in reducing ICU and hospital LOS [143]. Avoiding postoperative complications such as bleeding, arrhythmias, cardiogenic shock, and renal failure is essential.

KEY POINTS: BENEFITS OF FAST-TRACKING

- Many of the benefits associated with fast-tracking are related to earlier patient mobilization, and shorter ICU and hospital LOS.
- Reducing hospital-acquired infections by reducing LOS is one of the main reasons for implementing fast-tracking, particularly in developing countries.
- There are increasing data supporting the proposition that fast-tracking reduces costs.

Concerns and safety of fast-tracking

While fast-tracking and early extubation can certainly be accomplished in children undergoing CHS, the debate continues as to whether such an approach is safe and whether it offers benefits over a traditional approach [144–146]. The individual patient's response to CPB is unpredictable. The release of inflammatory mediators, the severity of lung injury, and changes in PVR are among many of the factors frequently cited in the discussion regarding early extubation. It must be noted, though, that improvements in the CPB technique help reduce the inflammatory response. Additionally, modern anesthetic agents, including short-acting opioids, allow for adequate blunting of inflammatory mediator release without compromising an early extubation strategy. Concerns about the lack of data from randomized prospective studies show clear benefits of fast-tracking and early extubation add further to the controversy. Some of the controversies come from the poorly defined definition of fast-tracking and early extubation. Early extubation is typically part of a fast-tracking approach to patient care with defined goals. However, this does not imply compromising patient safety, which has been clearly demonstrated in adult cardiac surgery where fast-tracking is almost uniformly practiced. Early extubation should be viewed as reducing unnecessary time on MV, rather than removing the endotracheal tube regardless of the underlying patient's condition. Commonly acknowledged extubation criteria, including adequate lung mechanics and oxygenation, and hemodynamic stability also apply to patients who are considered candidates for fast-tracking and early extubation. This is regardless of whether the endotracheal tube is removed at the end of the procedure in the OR, or after a certain time in the ICU. For example, low cardiac output and decreased left ventricular function following CPB are usually considered contraindications for early extubation. MV decreases oxygen consumption and workload of the heart and is considered beneficial by many practitioners in this setting. If responsive to low inotropic support, however, mild cardiac dysfunction does not need to be an absolute contraindication for early extubation and many of these children can be fast-tracked.

At this point, there is good evidence from multiple retrospective [17, 19, 26, 30] as well as prospective observational studies that fast-tracking can be accomplished safely even in CHS [34]. Preisman et al. randomly allocated 100 consecutive children (aged 1 month–15 years) presenting for CHS to anesthetic management aiming for fast-tracking and OR extubation or to a traditional approach with elective postoperative prolonged MV [31]. There was no significant difference in mortality, reintubation rate, reoperation for bleeding, infection, and other miscellaneous complications. The authors do acknowledge, though, that the study was not adequately powered to conclusively comment on the safety of fast-tracking, something that could only be accomplished with a large multicenter study. A meta-analysis of available studies on early extubation concluded that early extubation is associated with lower ICU and hospital LOS without increased morbidity or mortality [13].

Another measure of the safety of early extubation in CHS is the reintubation rate. As mentioned earlier, reintubation rates reported in the literature are low and they do not differ from those in fast-tracked patients. Mild respiratory acidosis is frequently encountered in children who have been extubated early. This is typically well-tolerated, normalizes within a few hours, and reintubation for respiratory depression is rarely necessary [21, 25, 26, 28, 30, 39, 114]. In case of mild airway obstruction or diminished respiratory effort, non-invasive respiratory support such as nasal continuous positive airway pressure (CPAP) can be advantageous for a few hours following extubation. The use of CPAP preserves the advantages of spontaneous ventilation and helps avoid reintubation.

Additionally, hospital readmission rates and mortality need to be considered when assessing the safety of fast-tracking CHS patients. Laurence et al. found no significant change in hospital mortality, and 2-week readmission rates were unchanged after implementing fast-tracking at their institution and were not different from the reported national rates [140].

KEY POINTS: CONCERNS AND SAFETY OF FAST-TRACKING

- Published data on fast-tracking support the safety of this strategy in CHS as well.
- Reintubation and readmission rates are similar to non-fast-tracked patients.
- Side-effects of early extubation, such as mild hypercapnia, are usually transient and well-tolerated.

Postoperative considerations

The multidisciplinary approach required for the success of fast-tracking CHS patients is particularly important in the postoperative arena, and the individual roles of all team members cannot be overemphasized. In general, standard postoperative considerations also apply to CHS patients who are fast-tracked and include adequate pain control and sedation without compromising respiratory parameters. Adequate pain control without compromising respiratory effort shortly after surgery is key to the success of an early extubation strategy. This is typically accomplished with multi-modal pain management and by limiting opioid use. The American Association for Thoracic Surgery consensus document on enhanced recovery after pediatric cardiac surgery also emphasizes the increasing role of opioid-sparing strategies [10]. Pain management strategies recommended include patient and family education, non-opioid analgesics, regional anesthesia, all a class IIa recommendation, as well as neuraxial techniques (IIb).

Intravenously administered opioids have been the mainstay of any pain regimen following surgery, including patients who are fast-tracked. Intravenous acetaminophen has analgesic as well as antipyretic effects [147]. It is currently FDA-approved for use in children older than 2 years [148], but off-label use in younger children is almost

ubiquitously practiced. Acetaminophen use for pain control seems attractive for fast-tracking as it does not cause respiratory depression, hemodynamic instability, platelet dysfunction, or potential kidney injury. However, there is currently limited experience with parenteral application in the pediatric cardiac surgery setting in the United States [149]. Although not usually associated with serious hemodynamic effects, mild hypotension, that is, mean arterial pressure decrease 15% from baseline, was seen in 5% of critically ill children with cardiac disease [150]. Hepatic injury is a known serious side effect, and pediatric dosing and contraindications should be carefully considered. Systemic clearance in neonates and young infants is significantly reduced. Dose reductions of 33% (age, 1 month to <2 years), and 50% in neonates up to 28 days, are recommended by the drug manufacturer. Other IV non-steroidal anti-inflammatory drugs (NSAIDs), such as ketorolac and indomethacin, have been linked to side effects such as gastrointestinal bleeding, bronchospasm, and kidney injury, which is why their use is somewhat restricted in the cardiac surgery setting. In a small prospective study in children undergoing CHS, the use of ketorolac was not found associated with adverse events [151]. Similarly, in a retrospective study in 67 patients undergoing CHS, the use of NSAIDs including acetaminophen and ketorolac was associated with lower pain scores and morphine requirements, and no increase in renal dysfunction and bleeding was noted [152]. A large systemic review found inconclusive data to support or reject the use of ketorolac for postoperative pain in children [153]. Despite the acknowledged knowledge gap regarding the safety of ketorolac in pediatric cardiac surgery [154], ketorolac is frequently used in a multi-modal opioid-sparing pain management regimen. The use of dexmedetomidine in CHS has been discussed earlier. As part of a fast-tracking strategy, it can help lower opioid use also in the postoperative period. In a large systemic review including five randomized controlled and nine observational studies and a total of 2,229 patients, dexmedetomidine was associated with lower requirements of postoperative fentanyl and morphine [155]. Dexmedetomidine is also frequently used for sedation in children following CHS [156–159]. It allows for sedation without significant respiratory depression and appears to be safe for use even beyond 24 hours; however, conclusive data from large randomized controlled studies are still lacking [160].

In the setting of fast-tracking, it is particularly important to differentiate between emergence delirium or agitation and inadequate pain control, particularly in infants and small children. The presence of parental support cannot be underestimated also for sedation and pain management purposes. Early extubation and mobilization allow for early parental engagement.

Neuraxial techniques

The addition of neuraxial techniques for pain management is advocated by some practitioners, while others vehemently oppose any neuraxial manipulation in patients undergoing CHS with CPB and full heparinization [161, 162]. Concerns persist about the safety of neuraxial manipulation in patients who are subsequently fully heparinized. Nevertheless, there is evidence that a neuraxial technique can be used safely and may offer benefits in the cardiac surgery setting. Epidural (including caudal) as well as intrathecal, single-shot, and continuous catheter techniques are used. While a thorough review of the individual techniques would go beyond the scope of this text and has been presented in detail elsewhere [163, 164], each individual technique will be discussed in relation to benefits, concerns, and evidence regarding safety and outcome in the pediatric cardiac surgery setting. The use of neuraxial anesthesia in CHS studies is presented in Table 24.2. As data on the safety in patients undergoing CHS are limited, references from large prospective studies in the adult cardiac population providing further insight into the matter are also included in the following sections.

Single-shot neuraxial techniques

Single-shot caudal techniques offer the advantage of simplicity and avoidance of manipulating a catheter in the epidural space. However, for procedures at the thoracic level, large volumes and higher doses of local anesthetics would be required to reach an adequate level from a caudal approach [168, 178]. Even then, the analgesic effect from a single shot local anesthetic would not last far into the postoperative period. Consequently, single-shot caudal techniques include or are often limited to the administration of an opioid; most commonly, preservative-free morphine. Morphine administered via the caudal space exhibits its peak analgesic effect within 4–7 hours [179] and its duration of action has been reported up to 24 hours [166, 180]. Typically, up to 100 μg/kg of preservative morphine is administered into the caudal space, with dose adjustments in the very young. Hydromorphone has also been tested, resulting in good pain control, and lower rates of opioid-related side effects have been suggested; however, data are very sparse at this point [181, 182]. The analgesic effect of a single-shot caudal is somewhat less predictable than a single-shot intrathecal technique. This is probably due to septations in the caudal epidural space, and a higher failure rate mostly from inadvertent subcutaneous rather than epidural injection [183]. In a prospective randomized controlled study in 50 children undergoing CHS, the caudal epidural was compared to intravenous analgesia [177]. The hemodynamic response to surgery was less pronounced and pain scores were lower in the caudal group. A large systematic review of caudal anesthesia in CHS patients identified a total number of 2,159 patients from 17 studies [184]. There was significant heterogeneity with regard to intervention and study population. Lower pain scores and a possible reduction in stress response were noted in some studies; although, the overall data were inconclusive to make firm recommendations for or against caudal anesthesia use. In older children, a single-shot subarachnoid (intrathecal) injection of preservative-free morphine (5–10 μg/kg) can easily be accomplished. Typically, 5 –10 mcg/kg of intrathecal morphine is administered, and higher doses (up to 30 mcg/kg have been reported) are associated with a higher incidence of respiratory depression [185, 186]. The use of intrathecal local anesthetics in children undergoing cardiac surgery, including high spinal anesthesia, has been described [167]. Hypotension is less frequently observed than adult spinal anesthesia [169];

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Table 24.2 Publications on neuraxial anesthesia in children undergoing congenital heart surgery

Reference	Study type	Patients enrolled	Neuraxial	Findings
Shayevitz et al. [165]	R	27/27	• Lumbar epidural catheter morphine infusion, vs. • IV opioid	• Shorter time to extubation, shorter ICU LOS, and earlier enteral feeding in the epidural group
Rosen & Rosen [166]	P/R	32 (2–12 years)	• Caudal morphine (75 μg/kg)	• Lower pain scores and less supplemental IV morphine in the caudal group
Hammer et al. [167]	R	25/25	• Single-shot intrathecal morphine (7–10 μg/kg) + tetracaine, vs. • Epidural catheter bupivacaine + hydromorphone (7–8 μg/kg)	• 100% extubation in OR in both groups, no reintubation • Patients with single-shot required more sedative/analgesics
Peterson et al. [114]	R	220	• Single-shot epidural, intrathecal, and epidural catheter techniques	• 89% extubated in OR, eight reintubations • Less adverse effects with thoracic epidural
Rojas-Perez et al. [168]	P/R	15/15	• Caudal (bupivacaine + morphine) + GA, vs. • GA alone	• Shorter time to extubation in caudal group • Less intraoperative fentanyl requirement in caudal group
Finkel et al. [169]	P	30 (7 months–13 years)	• Intrathecal tetracaine + morphine	• Good hemodynamic stability with spinal anesthesia • 100% extubation in OR
Suominen et al. [170]	P/R/observer-blinded	35/36	• Intrathecal morphine (20 μg/kg) + GA, vs. GA alone	• Time to first IV narcotic dose longer, and total dose of IV morphine lower in intrathecal group • No difference in time to extubation and ICU LOS
Humphreys et al. [171]	P/R	30/30 (<2 years)	• Intrathecal catheter (24–48 hours) morphine (20 μg/kg) and bupivacaine + GA, vs. • GA alone	• Spinal anesthesia resulted in lower plasma norepinephrine, epinephrine, and lactate levels
Hammer et al. [172]	P/R	20/20	• Single-shot intrathecal morphine (7 μg/kg) + GA, vs. GA alone	• Lower pain scores in intrathecal group • No difference in adverse events
Leyvi et al. [173]	R	46/71	• Single-shot caudal (bupivacaine + 70–110 μg/kg morphine), vs. • GA alone	• No difference in ICU/hospital LOS and pain score • Shorter time to extubation and reduced time on mechanical ventilation in caudal group
Stuth et al. [174]	P/R/observer-blinded	64 (2–55 months) Stage 2 and 3 single-ventricle palliation	• Caudal group (100 μg/kg + bupivacaine), vs. • Control (placebo caudal) + postoperative IV morphine	• In extubated children, caudal morphine delayed the need for rescue morphine in stage 3 palliation only • No significant difference in overall morphine requirements between active and placebo group
El-Morsy et al. [175]	P/R/observer-blinded	60 (1–24 months)	• Thoracic epidural, vs. • Paravertebral catheter	• Comparable analgesia, pulmonary function, plasma cortisol levels • Higher failure rate and more complications in the epidural group
Nasr et al. [176]	P/R/observer-blinded	20/20	• Caudal bupivacaine + dexmedetomidine (0.5 μg/kg), vs.	• Serum cortisol levels lower in the dexmedetomidine group
Samantaray et al. [177]			• Caudal bupivacaine + fentanyl (1 μg/kg)	• Lower pain scores in dexmedetomidine group

R, retrospective; P, prospective; O, observational; GA, general anesthesia; ICU, intensive care unit; OR, operating room; LOS, length of stay.

however, the duration of the block for pain management is usually inferior to an epidural continuous technique and is thus very infrequently practiced.

In general, epidurally and intrathecally administered opioids have been shown to provide excellent analgesia [167, 187], blunt the stress response to surgery and CPB [188–190], improve pulmonary function [191], and reduce time on MV [122, 168, 173].

In addition to the already discussed use of local anesthetics and opioids, α_2-receptor agonists such as clonidine [192–194], and more recently dexmedetomidine [176, 195], ketamine [196, 197], and magnesium [198–201], have all been added to minimize side-effects from neuraxially administered opioids, such as respiratory depression, and to prolong analgesic effects. A systematic review of the current literature identified 20 randomized trials where clonidine had been added to local anesthetic for caudal regional anesthesia [202]. The addition of clonidine resulted in superior long-lasting pain control and fewer patients requiring rescue analgesics, with no significant difference in complications. A similar review with ketamine added to caudal local anesthetics produced similar findings; however, the authors also indicated

that the available data do not allow for conclusions regarding potential neurotoxic effects [203]. To date, the experience in the United States with these additives remains limited and they are not routinely used. Even though single-shot techniques may provide somewhat inferior pain control when compared with a thoracic epidural catheter technique, they are quite popular among many practitioners as single-shot techniques require less time and the potential risks associated with an indwelling catheter are avoided [204].

Catheter-based neuraxial techniques

Epidural catheter insertion for pain management in children undergoing CHS has been described. Similar to single-shot neuraxial techniques, however, there are concerns about the safety in the cardiac surgery setting. Consequently, while individual centers routinely use epidural catheters and report good outcomes in the CHS setting, others object to epidural catheter manipulation in this patient population. Regardless of this ongoing controversy, lumbar epidural, caudal epidural, thoracic epidural, paravertebral, and even subarachnoid catheter insertion [171] have been reported in children undergoing cardiac surgery [114]. Compared with single-shot neuraxial or IV analgesia, epidural catheter techniques promise superior analgesia [172]. Peterson et al., for example, compared caudal epidural, lumbar epidural, thoracic epidural, and intrathecal blocks using a combination of morphine or hydromorphone and local anesthetic [114]. The majority of patients were extubated in the OR, and the use of a thoracic epidural catheter technique provided superior pain control with overall fewer adverse events compared with other neuraxial techniques. It seems logical that injection at the thoracic level results in better analgesia for cardiac surgery, and catheter manipulation is minimized. Additionally, local anesthetic administration at the thoracic level provides the additional advantage of the sympathetic blockade and superior blunting of stress response otherwise not achieved by lower epidural single-shot opioid-only based techniques. The insertion of an epidural catheter at the lumbar or caudal level and advancement of the catheter cranially in order to achieve adequate blockade at the thoracic level are also being practiced [165, 205–209]. While this technique seems to offer the advantage of not manipulating a needle in the thoracic epidural space, the epidural canal is heavily vascularized and the risk of advancing a catheter over a longer distance may actually carry a higher risk of injuring an epidural vein compared with the thoracic approach. Also, the correct positioning of the catheter tip at the thoracic level is not always achieved without fluoroscopy and may explain why catheters placed in the thoracic region seem to provide superior pain control with fewer side effects. While there may be real and potential benefits to neuraxial catheter-based analgesia compared with an IV analgesic regimen, the logistics associated with epidural catheter insertion and management are significantly more complex. Unlike adults, children usually do not tolerate awake catheter insertion. Day-of-admission surgery is routinely performed in the United States and is part of fast-tracking CHS patients, preventing catheter insertion well ahead of surgery and systemic heparinization. Additionally, catheter removal in patients with ongoing coagulopathy after surgery is problematic. Even in patients with normal hemostasis, patient discharge from the ICU may be delayed for safe removal and subsequent observation. For many practitioners who oppose neuraxial and, in particular, catheter-based techniques in patients with subsequent full heparinization, the risks outweigh the potential benefits.

Potential benefits of neuraxial techniques

Some of the benefits have already been mentioned in the previous section and many are related to superior pain control and consequently reduction in systemically administered analgesic and sedation requirements. Several studies in patients undergoing CHS compared an IV pain medication regimen with a combined IV and neuraxial technique. Hammer et al. [167] performed a prospective, randomized trial in children undergoing CHS, assessing the effects of adding single-shot subarachnoid tetracaine and morphine to an inhalational/remifentanil anesthetic. The analgesic effects of subarachnoid morphine were long-lasting and 8- and 24-hour pain scores and fentanyl requirements in the postoperative period were significantly lower in the spinal group compared with IV fentanyl only. Similarly, Rojas-Perez et al. also found reduced fentanyl requirements in children undergoing cardiac surgery with caudal morphine and bupivacaine [168]. Suominen et al. [144] examined the effects of a single-shot subarachnoid morphine (20 μg/kg) bolus in children undergoing CHS. In this prospective, randomized, and observer-blinded study, intrathecal morphine was associated with superior pain control following surgery as evidenced by a longer time to first bolus administration and lower total IV morphine requirements. The IV drug-sparing effects were observed for 12 hours after surgery. Interestingly, intrathecal morphine was not significantly associated with earlier extubation and shorter time in the ICU, which is frequently shown with epidural anesthesia. Another prospective study in children undergoing stage 2 and 3 palliations for single-ventricle CHD compared a primarily caudal technique with an IV drug regimen [145]. Both parents and the postoperative care team were blinded to the analgesic regimen. The use of caudal morphine significantly delayed the need for postoperative rescue morphine only in stage 3 patients. Surprisingly, overall IV morphine requirements did not differ between the groups. Most studies in adult cardiac surgery confirm superior pain control with neuraxial anesthesia added to a general anesthetic [210–212].

Despite these findings, critics will rightfully say that adequate pain control can also be achieved with IV analgesic drug administration. What seems more important than actual pain control, however, is how the IV drug sparing effect translates into other outcome measures. For example, multiple studies report earlier extubation and less time on MV with neuraxial analgesia [168, 211–217], and associated benefits such as reduction in respiratory complications have been discussed in detail earlier in the chapter. Findings of earlier recovery of intestinal function with neuraxial anesthesia [218] may also translate to the CHS setting, particularly if patients are mobilized earlier and enteral feeding can be commenced. Additional information can be gained from the adult literature. A large meta-analysis that included 1,178 patients from 15 randomized trials examining the

effects of thoracic epidural anesthesia in CBP surgery found decreased pulmonary complications, dysrhythmias, and time to extubation [219]. While improved postoperative pulmonary function is also reported by several other adult studies [217, 220, 221], the largest prospective randomized trial to date was unable to demonstrate a benefit of neuraxial anesthesia in preventing pulmonary complications or mortality [222]. A meta-analysis by the same author, however, included 31 randomized controlled trials with a total of 3,047 patients, comparing outcomes in adult patients undergoing cardiac surgery with either general anesthesia alone or in combination with thoracic epidural anesthesia [223]. This analysis confirmed a risk reduction for respiratory complications and supraventricular arrhythmias. Another large (1,543 patients) retrospective propensity score-matched study, found intrathecal morphine to be associated with fewer pulmonary complications compared to intravenous analgesia [224].

The effect on ICU and hospital LOS is controversial, with some studies suggesting reduced LOS with a neuraxial technique [225], while others did not observe a difference [212, 215, 216, 226–228]. A large prospective observational study in adult cardiac surgery patients compared general anesthesia supplemented with a thoracic epidural technique with general anesthesia alone. The addition of thoracic epidural anesthesia resulted in a shorter time on MV and fewer postoperative complications, such as delirium, pneumonia, acute renal failure, and myocardial function, resulting in shorter ICU LOS as well as reduced cost [225].

Additional benefits of neuraxial anesthesia include blunting of the inflammatory response to surgery and CPB. In children undergoing CHS, plasma norepinephrine and epinephrine concentrations [171] and 24-hour urinary cortisol excretion [229] were reduced with intrathecal drug administration. Additional benefits reported are less inotropic support requirements and greater hemodynamic stability [230], fewer arrhythmias [212, 217, 231], and improved ventricular function [232]. Data on biomarkers of myocardial injury in adult cardiac surgery were reduced in some studies [233], while others did not observe any difference when an epidural catheter was used [234]. Lee et al. [235] found that a total spinal with subarachnoid bupivacaine before induction of general anesthesia in adult cardiac surgery patients resulted in less β-receptor dysfunction in response to CPB, lower catecholamine levels, a higher cardiac index, and a lower PVR index in the post-CPB period. In adults undergoing cardiac surgery, the thoracic epidural blockade has also been shown to enhance coronary perfusion [236–239]; however, it is unclear if all these findings from the adult literature on neuraxial anesthesia can be transferred to children undergoing CHS.

Overall, the majority of studies in children as well as adults suggest that there are benefits in adding a neuraxial technique to the anesthetic regimen in patients undergoing cardiac surgery. Benefits supported by best evidence include superior pain control, less time on MV, and possibly fewer arrhythmias. With these and many of the additional benefits in mind, adding a neuraxial technique to the anesthetic regimen seems to be suited to facilitate fast-tracking CHS patients.

Risks and complications of neuraxial techniques

Many of the typical side effects of neuraxial anesthetics are not specific to cardiac surgery. Hemodynamic side-effects such as hypotension and bradycardia typically seen with neuraxially administered local anesthetics in adults are less pronounced in children [240]. Nausea and vomiting occur less frequently and prevention with commonly used drugs such as serotonin 5-HT3 receptor antagonists or a combination of drugs should be considered if very early extubation is planned [241]. Pruritus occurs in a very high percentage of cases, especially following intrathecal opioid administration. Diphenhydramine is a popular first-line choice for treatment. Its effectiveness for pruritus related to neuraxial opioids is limited, however, and small amounts of naloxone [242] or even mild sedation, for example, with dexmedetomidine [243] or small amounts of propofol [244] are often more effective choices. Mild respiratory depression is common with neuraxial opioid administration. Mild hypercarbia and respiratory acidosis are frequently seen, especially following early extubation; however, this is usually very well tolerated and rarely requires reintubation. Close observation in a monitored unit is recommended for 24 hours after neuraxial morphine administration, which is rarely a problem in children undergoing CHS. CPAP can be applied nasally or via facemask to support respiratory efforts. Urinary retention is not a problem in this patient population as almost all cardiac patients, including children, have a urethral catheter inserted. Ideally, all neuraxially administered drugs should be labeled for neuraxial use by the manufacturer. Particular attention should be paid to avoid drugs with added preservatives, some of which have been found to be neurotoxic when injected via the neuraxial route [245]. Few drugs are approved specifically for neuraxial administration; however, off-label use is common.

The most feared complication of a neuraxial regional anesthetic technique is an epidural hematoma. This is of particular concern in patients eventually undergoing full heparinization for CPB. Unlike in adults, the preoperative insertion of an epidural catheter in an awake child is rarely possible. Typically, neuraxial techniques are performed in the anesthetized child, prohibiting patient feedback during needle and catheter manipulation as well as injection. In order to perform a neuraxial technique safely, common considerations for neuraxial anesthetics must be followed, and careful attention to the most recent guidelines on neuraxial anesthesia in the setting of anticoagulant and antiplatelet agents is of paramount importance. Guidelines are published and regularly updated by the American Society of Regional Anesthesia (ASRA) [246]. Currently, the recommended time interval between neuraxial manipulation and full heparinization is 60 minutes. In practice, heparin is often administered earlier. For example, Weiner et al. [247] reviewed the medical records of 714 children who underwent CHS and who had either single-shot caudal or intrathecal morphine as part of their anesthetic regimen (no catheter insertion). There were no cases of symptomatic spinal or epidural hematomas. Further analysis showed that the time interval between full heparinization and neuraxial technique was less than 1 hour in 466 patients. Specifically, 299 patients were heparinized less than

45 minutes following neuraxial technique, including 270 caudal and 29 spinal morphine administrations; in 86 patients, heparin was given less than 30 minutes after the neuraxial technique. While this case series is too small to draw conclusions about the safe timing of single-shot neuraxial anesthesia and consequent heparinization, it provides further support that as long as the coagulation system is intact neuraxial manipulation can be performed safely. To date, there has only been one case of epidural hematoma reported in pediatric patients undergoing CHS. Rosen et al. reported a case of an adolescent who developed an epidural hematoma 2 days after surgery and epidural catheter placement. With the catheter still *in situ*, IV heparin was started for prosthetic valve thromboprophylaxis, and alteplase was administered additionally for management of a thrombosed central venous line [248]. The same group reviewed 750 records of children (52% infants) undergoing CHS who also had an epidural catheter placed as part of their anesthetic regimen and did not find any further neurologic complications [39].

While under-reporting may occur, the actual number of cases performed in clinical practice also far outweighs published case numbers. Given the very low incidence of this serious complication, it would require well-designed prospective studies with thousands of patients for an accurate risk calculation. To better assess current practice and the risk of neuraxial anesthesia in children, a multicenter database was created [249]. The Pediatric Regional Anesthesia Network database (PRAN) is a large multicenter registry collecting data on regional blocks performed at the participating institutions. The latest report from that database included over 104,393 blocks placed in children of all age groups, including 18,065 continuous catheters placed [250]. The majority of blocks (93.7%) were placed with the patient under general anesthesia. No permanent neurological complications were noted, and the risk of transient neurological deficits was calculated as 2.4:10,000 (95% CI, 1.6 to 3.6:10,000), with no difference between peripheral and neuraxial blocks. There were no cases of epidural hematomas seen with neuraxial catheters; one epidural hematoma was reported with a paravertebral catheter, and one epidural abscess was documented. From the same registry, Suresh et al. [251] focused on the safety of caudal blocks in children. Of the 18,650 children included, the estimated incidence of complications was estimated to be 1.9% (95% CI, 1.7–2.1%). Although this incidence seems relatively high, it must be noted that complications included the reporting of block failure, and otherwise were defined as blood aspiration, intravascular test dose injection, dural puncture, seizure, cardiac arrest, sacral pain, or neurological symptoms. No cases of permanent sequelae from complications were noted. Two additional large-scale reviews are also worth mentioning, even though they did not specifically target cardiac surgery cases. Participating centers in France submitted data on regional anesthesia in children over a 1-year period [252]. Data on 31,132 regional anesthetics were collected and analyzed. The overall complication rate was 0.12%; most were minor, and none resulted in permanent neurological damage. In Britain, data on epidural catheter analgesia in children were collected over a 5-year period [253]. A total of 10,633 catheter insertions in children were reported. Serious complications occurred in five children (1/2,000) resulting in permanent damage in one child; low severity events were more frequent (1/189). Insertion of epidural catheters in neonates was associated with a higher risk.

Additional information can be gained from publications in adult patients undergoing cardiac surgery [254]. Chakravarthy et al. [255] presented an audit of 2,113 cardiac surgery thoracic epidural anesthesia cases over a 13-year period with no permanent neurologic deficits, a 0.9% dural puncture rate, and 0.2% transient neurologic deficits. Jack et al. published their experience of thoracic epidural catheter placement in 2,837 patients undergoing cardiac surgery [256]. No epidural hematoma was seen in this series. Similar results were reported by Royse et al. [257], who reviewed 874 cardiac surgery cases involving epidural anesthesia over a 7-year period with no complications attributable to epidural catheter use. Pastor et al. [258] reported 714 uneventful cases in patients undergoing CABG surgery over a 7-year period. Overall, there are only very few cases of epidural hematomas associated with epidural anesthesia reported in adult cardiac surgery [259]. The vast majorities of studies are reassuring and confirm the safety of neuraxial anesthesia in adult cardiac surgery [260–264].

Several attempts have also been made to statistically estimate the actual and presumed risk of an epidural hematoma in patients undergoing cardiac surgery. A widely quoted estimation of the risk of epidural hematoma with thoracic epidural anesthesia in patients undergoing cardiac surgery is 1 in 12,000, with 95% confidence intervals (CI) of 1:2,100 to 1:68,000, and 1 in 1,000 with 99% confidence [265]. A risk assessment in cardiac surgery including source data up to 2012 found the risk of catheter-related epidural hematoma estimated to be 1 in 5,493 (95% CI: 1/970–1/31,114), which is similar to the risk of catheter-related epidural hematoma in the general surgery population (1 in 6,628; 95% CI: 1/1,170–1/37,552) [266]. Intrathecal risks from a different older source of risk assessment are quoted as 1 in 3,610 and 1 in 2,400, respectively [267].

In reviewing neurological complications associated with neuraxial anesthesia beyond the CHS setting, very few cases of epidural hematomas associated with neuraxial anesthesia have been reported. Not all of them are related to neuraxial manipulation [268] and even spontaneous epidural hematomas without the use of anticoagulants occur [269–271]. A report of four cases of permanent neurological injury in children undergoing general surgery cases did not reveal a common denominator [271].

In summary, available data on the safety of neuraxial anesthesia in patients undergoing CHS suggest that these techniques can be performed with minimal risk as long as current guidelines are followed. Additionally, when planning for neuraxial anesthesia, medico-legal concerns should also be considered in some CHS with the known inherent risk of spinal cord injury (i.e., coarctation of aorta repair) [272].

Regional blocks

Regional blocks have seen an increase in popularity including in pediatric cardiac surgery. As part of a multimodal pain management regimen suggested benefits include the ability to provide analgesia with fewer side effects. In the American

Association for Thoracic Surgery document on enhanced recovery after pediatric cardiac surgery [273], peripheral regional anesthesia achieves a class IIa recommendation as an effective opioid-sparing modality in CHS. Neuraxial anesthesia is also recognized to help reduce opioid use in the perioperative period (class of recommendation IIb). However, avoiding any neuraxial manipulation make regional blocks a potentially safer option compared to epidural or spinal anesthesia techniques, especially with systemic heparinization required for cardiopulmonary bypass. It must be noted though, that at the point of this writing high-quality data from large, randomized trials regarding the safety of regional blocks in CHS are still missing.

Various regional techniques have been described, including interpleural infusion of local anesthetics [274, 275], and subcutaneous wound infiltration techniques [276]. However, the ultrasound-guided fascial plane blocks that have recently seen a significant increase in use will be presented in the following paragraphs. Blocks can be administered prior to surgical incision, or after surgery, and single-shot as well as catheter based techniques have been described.

The administration of local anesthetic at the sternum bilaterally in each intercostal space prior to sternotomy closure is typically referred to as *parasternal blocks* or *intercostal nerve block (ICNB)* and can easily be performed by the surgeon in the field. Chaudhary et al. conducted a double-blind randomized trial in 30 children undergoing CHS, comparing 0.08 mL/kg/space of 0.5% ropivacaine with 0.9% saline injected in five parasternal spaces on each side before skin closure [277]. They reported no complications, improved pain scores, less postoperative opioid requirement, and shorter time to endotracheal extubation. Although local anesthetic can also be deposited in each intercostal space ultrasound-guided after the closure of the sternotomy wound, fascial plane blocks are typically preferred [278]. These fascial plane blocks target the anterior cutaneous branches of the intercostal nerves 2–6 at the sternum. The fascial plane between the transverse thoracic muscle and internal intercostal muscles also referred to as *Transverse Thoracic Muscle Plane Block* (TTPB) (Figure 24.2), or more superficially the plane between the intercostal muscles and pectoralis major muscle (*Pecto-Intercostal Fascial Block, PIFB*) are targeted (Figure 24.3). These blocks are similar to a parasternal block with regards to the analgesic effect; however, require fewer injections due to the local anesthetic spread in a fascial plane rather than a single intercostal space. In a prospective, double-blind study 100 children undergoing sternotomy were randomized to TTPB using 0.2% ropivacaine versus normal saline [279]. Postoperative pain scores up to 24 hours, intraoperative fentanyl use, and postoperative rescue fentanyl requirements were lower in the ropivacaine group. These findings were confirmed in a similar prospective, randomized, double-blind study in 80 children aged 2–12 years undergoing cardiac surgery [280]. Care must be taken to avoid puncture and inadvertent injection of local anesthetic into the vascular bundle underneath the ribs, and the internal mammary artery, the latter of which descends along the chest wall in the same fascial plane used for the transversus thoracis muscle plane block (TTPB).

Paravertebral blocks [281, 282], as well as catheters [283], have also been used in children and CHS. El-Morsy et al. [284] performed a prospective randomized study comparing thoracic epidural with paravertebral catheter placement in 60 children (age 1–24 months) undergoing CHS. Analgesia, serum cortisol level, and pulmonary function parameters were comparable; however, failure rate and complications were more frequent in the epidural group. In a review of the literature and meta-analysis of epidural vs. paravertebral catheter insertion in adult patients undergoing thoracotomy, Davies et al. also found fewer side-effects such as nausea, vomiting, and hypotension associated with a paravertebral technique [175]. Data from 100 children undergoing CHS with a paravertebral block were reviewed and matched with a historical control group [285]. Pain scores, fentanyl use, and time to first rescue

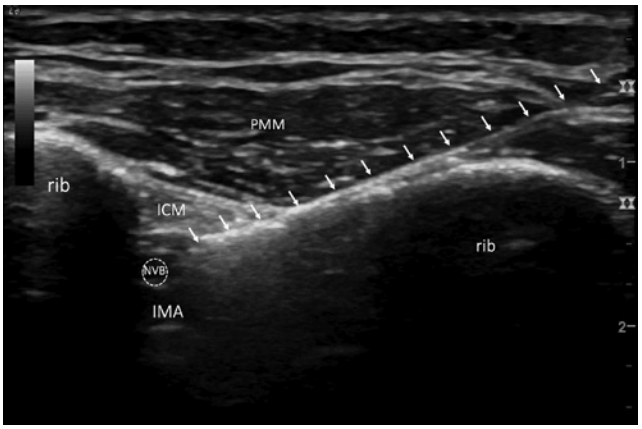


Figure 24.2 Ultrasound image of a *Transverse Thoracic Muscle Plane Block* (TTPB) in an adult patient. (A) PMM, pectoralis major muscle; ICM, intercostal muscle; IMA, internal mammary artery; NVB, neurvascular bundle.

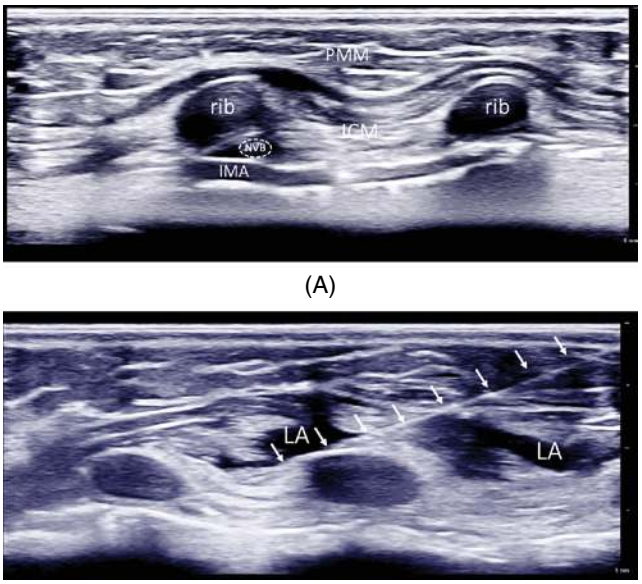


Figure 24.3 Ultrasound image of a Pecto-*Intercostal Fascial Block (PIFB)* in a 2-year-old patient. (A) PMM, pectoralis major muscle; ICM, intercostal muscle; IMA, internal mammary artery; NVB, neurovascular bundle. (B) Arrows indicate needle; LA, local anesthetic.

analgesic were all lower in the paravertebral block group. Limited information is available regarding the risk of developing a hematoma in anticoagulated patients after a paravertebral block. It has therefore been recommended to follow the same guidelines used for neuraxial blockade [246].

Recently, the *Erector Spinae Plane Block (ESPB)* has been the subject of a number of publications for thoracotomy and chest wall surgery, and as a bilateral block for sternotomy procedures [278] (Figures 24.4 and 24.5). The presumed mechanism includes diffusion of local anesthetic into the paravertebral space (posterior paravertebral pathway), as well as anterior spread reaching the lateral cutaneous nerve branches (lateral pathway) [286]. In a prospective, but not blinded study, 80 children were randomized to ultrasound-guided bilateral ESPB with 0.2% ropivacaine and a control group [287]. Postoperative pain scores were significantly lower in the block group up to 10 hours postoperatively. In another prospective, randomized, and double-blinded study using bilateral ESPB catheters in 50 children undergoing sternotomy, patients were randomized and received programmed intermittent boluses of 0.2% ropivacaine versus normal saline [288]. Postoperative pain scores and 48 hours cumulative morphine requirements were significantly lower in the ropivacaine group.

The *Serratus Anterior Plane Block (SAPB)* is another ultrasound-guided fascial plane block; however, its effect is limited to the lateral chest wall, that is, lateral cutaneous nerve, and does not reach the terminal nerve endings near the sternum (Figure 24.6). In CHS, indications for a SAPB may include a lateral incision for surgical closure of a persistent ductus arteriosus, coarctation of aorta, or any lateral chest wall approach to cardiac surgery [289–292]. In a prospective, randomized, single-blind study in 108 children undergoing CHS via a thoracotomy approach comparing ICNB, SAPB, and pectoral nerve block (PECS II), pain scores were similar in the three groups, with higher rescue fentanyl requirements in the ICNB [293]. Despite obvious limitations, the use of SAPB has been described for sternotomy in a small case series [294].

It must also be noted, that despite the promising results and most studies showing opioid-sparing effects, superficial plane blocks are best suited as part of a multimodal regimen, and rarely provide adequate analgesia when used alone. A systemic review including 14 randomized trials and 605 patients found regional anesthesia to help reduce pain up to 24 hours after cardiac surgery [295]. The effective reduction in pain was equivalent to 2.1–2.9 on a scale from 0–10. No significant effect on nausea and vomiting, and major morbidity and mortality were noticed. For single-shot techniques and administered after surgery, the analgesic effect typically lasts no longer than 12 hours, and this time can obviously be extended with catheter-based techniques. Deeper structures, referred pain, positional pain, chest tube insertion and pleural pain, are frequent sources of post-cardiac surgery pain. Often pain significantly subsides when chest tubes are removed in the postoperative course, demonstrating the limitation of regional blocks to the incision site. Chest tube pain can be somewhat mitigated by direct local anesthetic infiltration of the insertion sites, or a *Rectus Sheath Block (RSB)* has been described for that purpose [296].

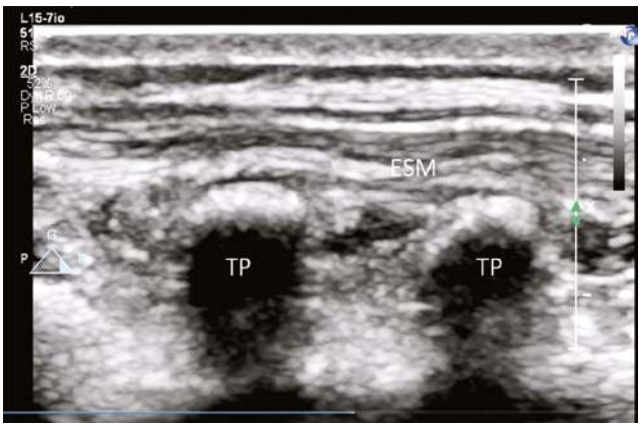


Figure 24.4 Ultrasound image of anatomy for Erector Spinae Plane Block (ESPB) in a 6-week-old patient. ESM, erector spinae muscle; TP, transverse process.

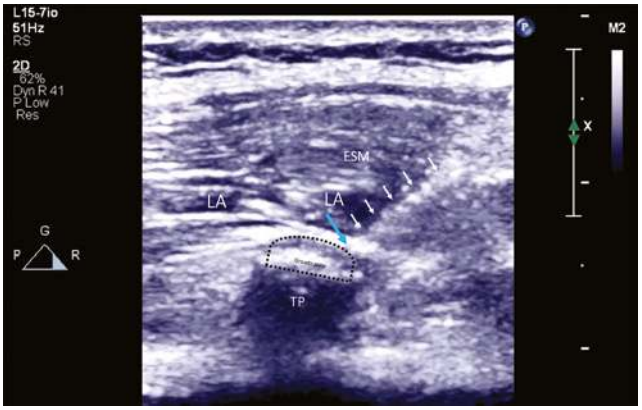


Figure 24.5 Ultrasound image of Erector Spinae Plane Block (ESPB) in a 5-year-old patient. White small arrows indicate needle shaft, blue arrow indicates needle tip in contact with the head of the transverse process. The growth plate can be seen as an echodense line below the tip of the transverse process. ESM, erector spinae muscle; LA, local anesthetic.

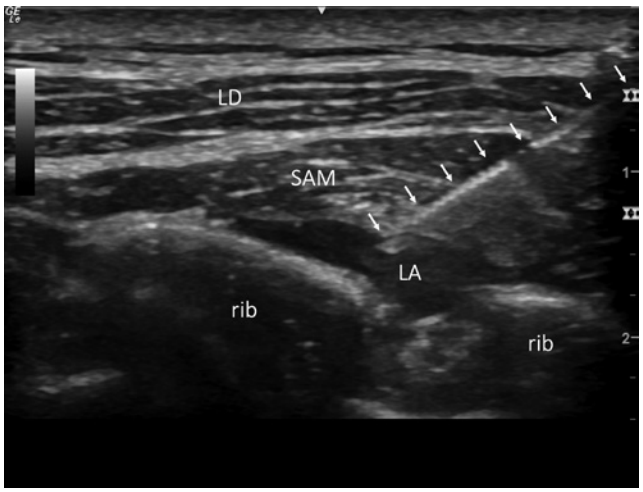


Figure 24.6 Ultrasound image of a serratus anterior plane block (SAPB) in an adult patient. LD, latissimus dorsi; LA, local anesthetic; SAM, serratus anterior muscle. Arrows indicate needle.

Other risks and limitations include the laterality of a regional block necessitating bilateral blocks for midline procedures, also possibly increasing the risk for local anesthetic toxicity. Reassuring data come from several studies, including a study in 27 children undergoing cardiac surgery with and without cardiopulmonary bypass. The use of bilateral ESPB catheters in these children did not lead to signs of clinical local anesthetic toxicity, and plasma lidocaine levels were below toxic thresholds in both groups [297]. Although regional blocks and in particular ultrasound-guided fascial plane blocks are considered a safer choice when compared to neuraxial techniques, for deeper blocks such as the ESPB, and blocks administered in areas with high vascularity, the current recommendations are to apply neuraxial guidelines [246].

The reader is referred to several excellent reviews for a more detailed discussion of neuraxial and regional anesthesia techniques [278, 298].

KEY POINTS: NEURAXIAL AND REGIONAL TECHNIQUES

- Multimodal pain management strategies include IV, as well as regional or even neuraxial techniques.
- Regional techniques and in particular ultrasound-guided fascial plane blocks are increasingly used as part of a multimodal pain management strategy.
- Neuraxial manipulation with subsequent systemic heparinization for CPB is controversial.
- There are increasing data showing that neuraxial techniques can be used safely in CHS.
- The benefits of neuraxial anesthesia beyond superior pain control are increasingly recognized.
- For deeper fascial plane blocks neuraxial guidelines should be applied.

Conclusions

Fast-tracking patients undergoing CHS has become a viable alternative to a more traditional approach of prolonged postoperative sedation and MV in CHS. Modern anesthetics allow early extubation and adequate pain control without compromising patient safety. In eligible patients, fast-tracking can offer benefits. The overall success of fast-tracking CHS patients requires careful patient selection, recognizing contraindications, and most importantly embracing the fact that this is a multidisciplinary approach that involves all specialties involved in CHS patient's care [299]. Each individual component is equally important for the success of implementing and maintaining fast-tracking in a CHS program.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

10 Fuller S, Kumar SR, Roy N, et al. The American Association for Thoracic Surgery Congenital Cardiac Surgery Working Group 2021 consensus document on a comprehensive perioperative approach to enhanced recovery after pediatric cardiac surgery. J Thorac Cardiovasc Surg 2021;162(3):931–54. Online ahead of print.PMID: 34059337. The American Association for Thoracic Surgery published a consensus document on enhanced recovery after pediatric cardiac surgery. Key strategies that were identified for successfully implementing and maintaining an enhanced recovery pathway include a multi-disciplinary approach, appropriate patient selection, staff and patient/family education, protocol, and guideline-driven practice. The task force concludes that enhanced recovery protocols do not increase morbidity and mortality after pediatric cardiac surgery. Patient and family satisfaction with perioperative care may be improved.

13 Alghamdi AA, Singh SK, Hamilton BC, et al. Early extubation after pediatric cardiac surgery: systematic review, meta-analysis, and evidence-based recommendations. J Card Surg 2010;25:586–95. Meta-analysis and review of the literature of early extubation in children undergoing CHS. Early extubation was associated with lower mortality, shorter ICU and hospital LOS, fewer respiratory complications, and lower costs.

21 Varghese J, Hammel JM, Ibrahimiye AN, et al. Outcomes related to immediate extubation after stage 1 Norwood palliation for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2019;157:1591–8. The feasibility of fast-tracking including early extubation in children has been demonstrated for most patients undergoing congenital heart surgery. This single-center series reports success in early extubation even after stage I Norwood palliation for hypoplastic left heart syndrome.

32 Kin N, Weismann C, Srivastava S, et al. Factors affecting the decision to defer extubation after surgery for congenital heart disease – a prospective observational study. Anesth Analg 2011;113:329–35. Prospective observational study to assess factors associated with OR extubation following CHS. Preoperatively known factors such as procedure complexity, CPB without aortic cross-clamping, age, and trisomy 21, were predictors of OR extubation.

55 Mahle WT, Nicolson SC, Hollenbeck-Pringle D, et al. Utilizing a collaborative learning model to promote early extubation following infant heart surgery. Pediatr Crit Care Med 2016;17:939–947. The Pediatric Heart Network Collaborative Learning Study used collaborative learning principles to implement early extubation guidelines across 4 active study sites and five control sites. Overall compliance with early extubation guideline adoption was high, and an increase in early extubation rates, from 11.7% before to 66.9% at the active sites, were seen for patients undergoing tetralogy of Fallot repair after guideline implementation. No change was noted for coarctation of aorta repair. There was no increase in the reintubation rate during the study period.

126 Ono M, Georgiev S, Burri M, et al. Early extubation improves outcome following extracardiac total cavopulmonary connection. Interact Cardiovasc Thorac Surg 2019;29(1):85–92. In patients with single-ventricle physiology undergoing bi-directional Glenn or Fontan procedure, early extubation and spontaneous ventilation have been associated with improved hemodynamics. This paper reports additional benefits including lower inotropic support, earlier chest tube removal, and shorter ICU LOS. Lower intrathoracic pressure associated with spontaneous ventilation increases central venous blood return, which becomes the driving force of pulmonary blood flow across the pulmonary vascular bed and thus for maintaining left ventricular preload and cardiac output.

135 Kawaguchi A, Liu Q, Coquet S, et al. Impact and challenges of a policy change to early track extubation in the operating room for Fontan. Pediatr Cardiol 2016;37:1127–36. An examination of the impact of an institutional policy change to early extubation in patients undergoing Fontan palliation. The policy change was associated with an impressive reduction in ICU LOS (average 4.1 days; 95% CI −1.2 to −6.9). Fluid balance did not differ, and although the rate of reintubation was statistically not different, hemodynamic

instability was the main reason for reintubation prior to policy change, and bleeding and respiratory etiology listed most commonly in the time period after.

140 Lawrence EJ, Nguyen K, Morris SA, et al. Economic and safety implications of introducing fast tracking in congenital heart surgery. Circ Cardiovasc Qual Outcomes 2013;6:201–7. The impact of implementing fast-tracking, including early extubation in patients undergoing CHS, was assessed and compared with a nationwide cohort. Shorter LOS and cost savings compared with national data were observed after the implementation of fast-tracking.

278 Mittnacht AJC, Shariat A, Weiner MM, et al. Regional techniques for cardiac and cardiac-related procedures. J Cardiothorac Vasc Anesth 2019;33:532–46. A comprehensive modern review of regional techniques, including erector spinae, serratus anterior, pectoral, and transversus thoracic plane blocks.

288 Macaire P, Ho N, Nguyen V, et al. Bilateral ultrasound-guided thoracic erector spinae plane blocks using a programmed intermittent bolus improve opioid-sparing postoperative analgesia in pediatric patients after open cardiac surgery: a randomized, double-blind, placebo-controlled trial. Reg Anesth Pain Med 2020;45:805–12. A prospective, randomized, and double-blinded study using bilateral erector spinae plane block catheters in 50 children undergoing sternotomy, patients were randomized and received programmed intermittent boluses of 0.2% ropivacaine versus normal saline. Postoperative pain scores and 48 hours cumulative morphine requirements were significantly lower in the ropivacaine group.

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CHAPTER 25

Cardiopulmonary Resuscitation in the Patient with Congenital Heart Disease

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Epidemiology

Although one of the most severe of adverse events related to anesthesia, cardiac arrest (CA) in the perioperative setting occurs infrequently, with rates of anesthesia-related CA during pediatric anesthesia in the general population reported between 0.14 and 0.8% of anesthetics [2–4]. Significant variability in anesthesia-related CA rates exists across the pediatric age and illness category spectrum; yet, there is clear evidence to support higher risks of periprocedural CA for patients with underlying CHD [5]. Children with CHD frequently undergo diagnostic and interventional procedures that require sedation or general anesthesia with over 45,000 noncardiac [6] and over 25,000 cardiac [7] surgical procedures performed every year across North America. In spite of these yearly procedural volumes for the CHD population, our understanding of the epidemiology and outcomes after anesthesia-related CA remains limited to historical reports from CA registries and single-center case series [6, 8, 9]. Clear limitations exist with volunteer registry reporting, including potential underreporting of events, which limits our understanding of true incidence as well as the risks associated with anesthesia during pediatric cardiac surgery, cardiac catheterizations, and noncardiac procedures in the CHD population.

Over the last three decades, several single and multicenter retrospective cross-sectional efforts have provided a basic foundation for our understanding of the incidence and potential risk factors associated with anesthesia-related CA in the CHD population. The Pediatric Perioperative Cardiac Arrest (POCA) registry, formed in 1994 to study the etiology and outcomes after perioperative CA in anesthetized children, has published two reports that focused on anesthesia-related CA which spanned the first 10 years of this registry [2, 8]. Of 373 cases of anesthesia-related CA reported to the registry between 1994 and 2005, 34%

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(n = 127; acquired conditions included cardiomyopathy, pulmonary hypertension, arrhythmias, status-post heart transplantation) were in children with congenital and/or acquired heart disease, of which 92% were in children with the American Society of Anesthesiologists (ASA) physical status III–V compared to 62% in children without heart disease. Of note, 47% of all CAs in children with CHD and acquired lesions occurred at the age of 6 months or younger, and 70% occurred in children aged ≤2 years. A slight majority of CAs occurred in the general operating room (OR) setting (54%) as compared to the cardiac OR (33%), cardiac catheterization laboratory (17%), and other imaging suites (3%). Again, younger age (<6 months old) was more commonly seen in the cardiac OR CA population (76%) as compared to general OR (38%) or catheterization laboratory (35%) [8]. In children with heart disease, those with single ventricle composed 19% of CAs, closely followed by patients with left-to-right shunts (e.g. VSD, PDA, AV canal, combined lesions; 18%), left-sided obstructive lesions (e.g. aortic stenosis, coarctation of the aorta; 16%), acquired conditions (13%), Tetralogy of Fallot (12%), Truncus arteriosus (5%), and miscellaneous conditions (e.g. pulmonary hypertension, status-post heart transplant, arrhythmias; 18%). Overall mortality in the heart disease CA population was 33%, with the highest mortality in left-sided obstructive lesions and cardiomyopathy. Resuscitation details available for 68 patients with congenital and/or acquired heart disease revealed few instances of the use of extracorporeal cardiopulmonary resuscitation (E-CPR; n = 3), which would suggest lack of availability of this resource in many centers in the 1990s and early 2000s. Current evidence suggests that patients with underlying cardiac disease are the highest utilizers of E-CPR [10], with an epidemiologic report of CA in the cardiac intensive care unit (CICU) from the Pediatric Cardiac Critical Care Consortium (PC^4) reporting 27.2% of all CAs occurring in participating CICUs undergoing E-CPR [11].

Amongst single-center reports, Boston Children's Hospital has maintained an extensive registry of CHD patients anesthetized in cardiac operating room and catheterization laboratories with reported frequencies of 0.79% (during cardiac surgery) and 0.96% (during cardiac catheterizations) [4, 12]. Within the cardiac catheterization laboratory, recent efforts to evaluate outcomes after risk adjustment have led to the inclusion of CA as a part of a larger group of severe adverse events (AEs) [13, 14]. These efforts have confirmed the findings by Odegard et al. that CA occurs infrequently during pediatric diagnostic and interventional catheterizations (0.8-1.6%). Furthermore, in an analysis of the American Heart Association (AHA)'s Get With the Guidelines-Resuscitation registry of in-hospital cardiac arrest (IHCA) across 33 pediatric hospitals between 2005 and 2016, Lasa et al. described results of CA occurring in the cardiac catheterization laboratory by evaluating survival to hospital discharge and favorable neurologic outcomes [15]. Of 19,957 pediatric IHCA events, only 203 index CAs were reported to the registry as occurring within the cardiac catheterization laboratory. The survival to discharge rate for the overall cohort was 69% (141/203), of which the majority (69%) of deaths were observed in children <1 year of age.

KEY POINTS: EPIDEMIOLOGY OF CARDIAC ARREST IN CHD

- Cardiac arrest (CA) that occurs in the periprocedural arena related to anesthesia is an infrequent event occurring in 0.14–0.80% of anesthetics.
- Children with underlying congenital and/or acquired heart disease are at a higher risk for CA with rates ranging from 0.8 to 1.0%, although limited by single center and/or historical registry data sources.
- Within the CHD population, patients who are younger and/or with single ventricle anatomy/physiology are at the highest risk for periprocedural anesthesia-related cardiac arrest.

Overview of current CPR guidelines

Since serving as a co-sponsor for the inaugural gathering of resuscitation researchers and healthcare providers at the Conference on Standards and Guidelines for Cardiopulmonary Resuscitation and Emergency Care in 1966, the AHA has continued to publish guidelines on the performance of CPR for both adult and pediatric patient populations. From 2015, the process of 5-year updates was transitioned to an online format to allow significant changes in the science to be reviewed in an expedited manner and then incorporated directly into the guidelines if deemed appropriate.

AHA has released the latest 2020 guidelines with 491 updated recommendations for adult, pediatric and neonatal life support. For the purpose of the pediatric advanced life support guidelines, pediatric patients are infants, children, and adolescents up to 18 years of age, excluding newborns. Infant guidelines apply to infants younger than 1 year of age. Child guidelines apply to children from approximately 1 year of age until puberty. For those with signs of puberty and beyond, adult basic life support guidelines should be followed. Although pediatric IHCA outcomes have improved steadily since 2004, similar gains are not being seen in out-of-hospital cardiac arrest (OHCA). Much of the variation in survival rates is thought to be due to the strength of the chains of survival, the critical actions that must occur in rapid succession to maximize the chance of survival from CA (see Figure 25.1) [16]. A separate OHCA chain of survival has been created to distinguish the differences between OHCA and IHCA. In both the chains, a sixth link has been added to stress the importance of recovery [16].

The major new and updated recommendations in 2020 can be seen in Table 25.1 [16]. Rapid recognition of CA, immediate initiation of high-quality chest compressions, and delivery of effective ventilations are critical to improve outcomes from CA. The 2020 AHA recommendations for high-quality CPR can be seen in Table 25.2 [16]. New changes to ventilation rates include increases in recommended respiratory rates to 20–30 breaths/min for infants and children with an advanced airway during CPR or for those requiring rescue breathing with a pulse. The Pediatric Cardiac Arrest Algorithm as updated in the AHA 2020 Guidelines is also available in Figure 25.2 [16].



(A)



(B)

Figure 25.1 Pediatric chains of survival for out-of-hospital (A) and in-hospital (B) cardiac arrest. (Source: Topjian et al. [16]. Reproduced with permission from Wolters Kluwer Health, Inc.)

Table 25.1 Key CPR guidelines recommendations and differences noted between 2010 and 2020 publications

Guidelines/recommendations	2010	2020
Assisted ventilation rate: rescue breathing – in conditions where there is a palpable pulse but inadequate breathing.	Rate of 12–20 (One breath every 3–5 seconds)	Rate of 20–30 breaths/min (One breath every 3–5 seconds)
Ventilation rate during CPR with an advanced airway	10 breaths/min (one breath every 6 seconds)	20–30 breaths/min accounting for age and clinical conditions.
Endo-tracheal tubes (ETT)	Both cuffed and uncuffed ETTs are acceptable for intubating infants and children.	It is reasonable to choose cuffed ETTs over uncuffed ETTs for intubating infants and children.
Cricoid pressure during intubation	Insufficient evidence to recommend	Routine use is not recommended.
Epinephrine administration	Reasonable to administer epinephrine in pediatric cardiac arrest	Reasonable to administer the initial dose within 5 minutes from the start of chest compressions.
Invasive blood pressure monitoring to assess CPR quality	Reasonable for providers to use diastolic blood pressure to assess CPR quality (>25 mmHg in infants, >30 mmHg in children)	Reasonable for rescuers to use diastolic blood pressure to guide CPR quality.
Detecting and treating seizures after ROSC	It is recommended to treat clinical seizures following cardiac arrest	When resources are available, continuous EEG monitoring is recommended for the detection of seizures following cardiac arrest in patients with persistent encephalopathy.
Evaluation and support for cardiac arrest survivors		Rehabilitation services are recommended for survivors. Ongoing neurological evaluation for at least the first year after cardiac arrest.

Source: Topjian et al. [16]. Reproduced with permission from Wolters Kluwer Health, Inc.

Table 25.2 Current CPR guidelines recommendations for all age groups

CPR guidelines	Infant	Children	Adult
Chest compression rate (per minute)	100–120	100–120	100–120
Depth of compression	One-third of AP diameter of chest (4 cm/1.5 in.)	One-third of AP diameter of chest (5 cm/2 in.)	At least 5 cm but not more than 6 cm (Once children have reached puberty)
Chest recoil	Allow the chest to recoil completely, after each compression		
Rhythm check	Lasting no more than 10 seconds, approximately every 2 minutes		
Respiratory rate with no advanced airway	Compression to ventilation ratio – single rescuer 30 : 2, two rescuers 15 : 2.		Compression to ventilation ratio – 30 : 2.
Respiratory rate with advanced airway	Reasonable to target respiratory rate of 1 breath every 2–3 seconds (20–30 breaths/min)		Provide breath every 2–3 seconds

Source: Data from Topjian et al. [16].

CPR techniques

For infants, single rescuers should compress the sternum with two fingers or two thumbs placed just below the intermammary line. For two rescuers, the two-thumb encircling hands technique is recommended. If the rescuer cannot physically encircle the victim's chest, the chest can be compressed with two fingers. If the rescuer is unable to achieve the guideline-recommended depth, it may be reasonable to use the heel of one hand. For children, it may be reasonable to use either a one- or two-hand technique to perform chest compressions.

Advanced airway interventions during CPR

For OHCA, studies show similar rates of survival to discharge when comparing advanced airway interventions such as supraglottic airway or endotracheal tube with bag-mask ventilation. Similarly, early placement of an invasive airway after IHCA was also not associated with improvement in survival to hospital discharge [17]. For IHCA there is insufficient evidence as of now to make any recommendation about advanced airway management [18].

Drug administration during CPR

The new guidelines emphasize administration of epinephrine within 5 minutes from the start of chest compressions with repetition every 3–5 minutes until the return of spontaneous circulation (ROSC) is achieved. For shock refractory ventricular fibrillation (VF)/pulseless ventricular tachycardia (pVT), either amiodarone or lidocaine can be used. Routine use of sodium bicarbonate and calcium is not supported by the current data unless their administration is indicated in specific circumstances such as electrolyte imbalances and certain drug toxicities. Table 25.3 lists pharmacologic therapy, indications, and precautions for resuscitation.

Management of ventricular fibrillation and/or pulseless ventricular fibrillation

Defibrillation is the definitive treatment of VF/pVT. An initial dose of 2 Joules per kilogram (J/kg) is recommended followed by an increase in the subsequent dose to 4 J/kg for the second shock. For subsequent shocks, higher energy levels may be considered but not to exceed 10 J/kg or the maximum dose for adults.

Pediatric resuscitation in patients with suspected or confirmed COVID-19 infection

Resuscitation in this population carries an added risk to healthcare workers as the chest compressions, positive pressure ventilation, and establishment of an advanced airway generate aerosols that can remain suspended in the air with a half-life of ~1 hour. These aerosols can be inhaled by those nearby. To mitigate the risk of exposure to healthcare workers, emphasis should be placed on donning personal protective equipment (PPE) before entering the operation room/scene and limiting personnel in the room to only those essential for patient care. If an advanced airway is considered, pause chest compressions for intubation and use the intubator with the highest likelihood of first-pass success. Intubate patients with a cuffed tube and connect the endotracheal (ET) tube to a ventilator with a high-efficiency particulate air (HEPA) filter when available [20]. Protection against inhalation of the aerosolized virus with N95 mask or equivalent, eye protection, gown, and double gloving is important for suspected or confirmed COVID-19 infection.

KEY POINTS: CPR GUIDELINES

- High-quality cardiopulmonary resuscitation (CPR) is the foundation of resuscitation including the provision of adequate chest compression rate and depth, minimizing interruptions in CPR, allowing full chest recoil between compressions, and avoiding excessive ventilation.
- New changes to ventilation rates include increases in recommended respiratory rates to 20–30 breaths/min for infants and children with an advanced airway during CPR or for those requiring rescue breathing with a pulse.

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Pediatric cardiac arrest algorithm

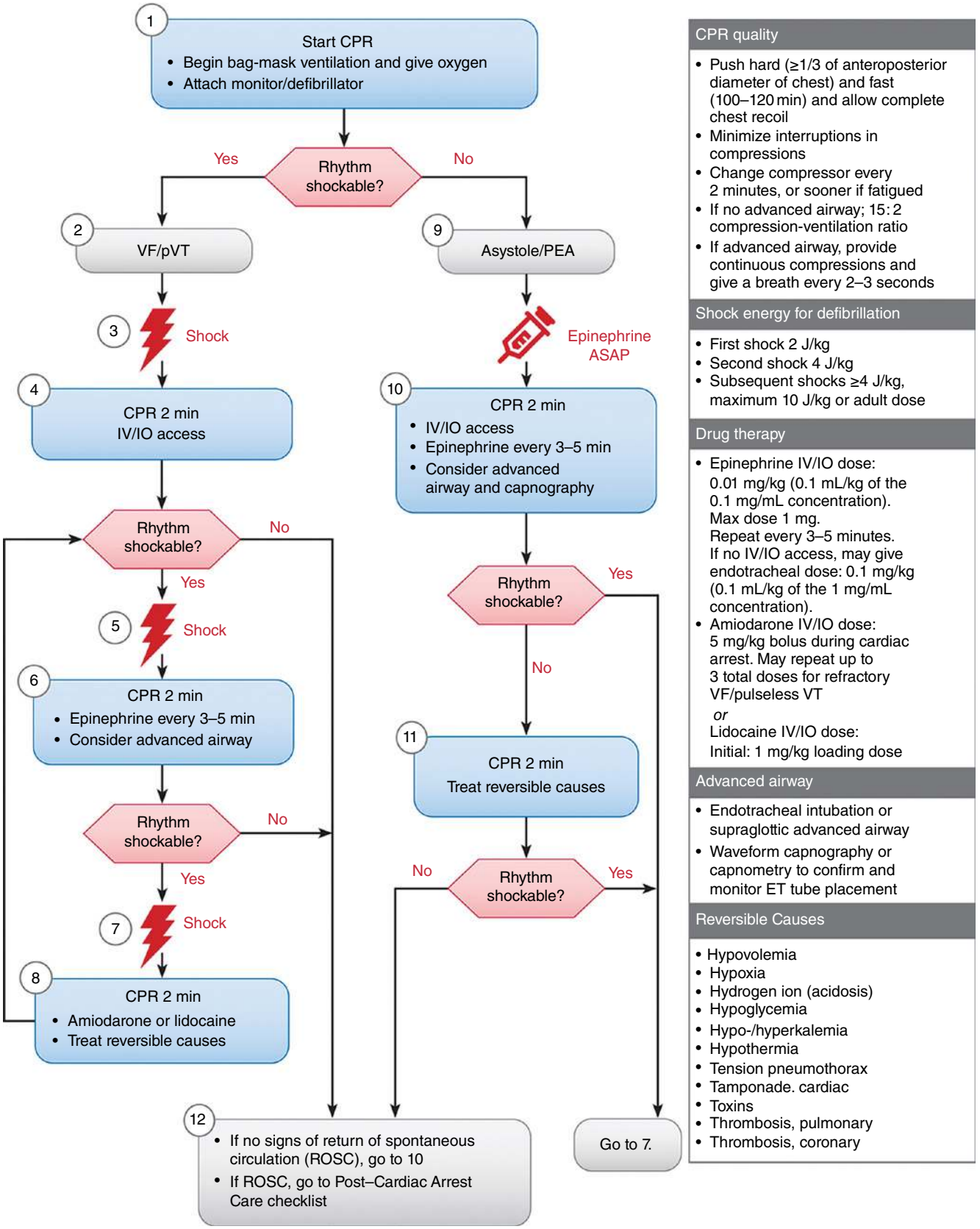


Figure 25.2 Pediatric cardiac arrest algorithm as updated in the American Heart Association 2020 guidelines. (Source: Topjian et al. [16]. Reproduced with permission from Wolters Kluwer Health, Inc.)

Table 25.3 Pharmacology: typical doses and indications

Medication	Dose	Indications	Cautions/precautions
Adenosine	Initial dose: 100 μg/kg (0.1 mg/kg; maximum single dose: 6 mg) rapid IV push; second dose can be double the first dose (i.e. give 200 μg/kg [0.2 mg/kg] for second dose, maximum 12 mg)	Atrioventricular node–dependent SVT	Adenosine will not effectively terminate atrioventricular node–independent tachycardias, such as atrial flutter, ectopic atrial tachycardia, or atrial fibrillation. Should not be administered for wide QRS complex tachycardia unless it is clear that the underlying rhythm is not atrial fibrillation or atrial flutter with associated antegrade accessory pathway conduction Expert consultation should be obtained before the administration of adenosine as a diagnostic and potentially therapeutic intervention for stable patients who have wide QRS complex tachycardia
Amiodarone	For VF/pulseless VT, in absence of known or suspected long-QT syndrome: Initial dose: 5.0 mg/kg IV/IO bolus. Maximum single dose: 300 mg; can repeat to a total of three doses; total: 15 mg/kg/24 hours; in adolescents, maximum 2.2 g/24 hours For perfusing atrial or ventricular arrhythmias: Give loading dose of 5 mg/kg over 30–60 minutes[a] Maximum single dose: 300 mg; can repeat to a maximum of three doses Total: 15 mg/kg/24 hours; in adolescents, maximum 2.2 g/24 hours If the patient is hemodynamically unstable or receiving other medications that lower heart rate, consider lower dose and slower infusion	Shock-refractory cardiac arrest (VF/pulseless VT); atrial and ventricular arrhythmias; JET	Use lower dose and/or slower infusion if the patient is hemodynamically unstable or receiving other medications that lower heart rate; can cause hypotension; can prolong QT interval: 1. Obtain expert consultation before administering, if known or suspected long-QT syndrome. 2. Routine administration in combination with procainamide or digoxin is not recommended without expert consultation
Atropine	For symptomatic bradycardia: 20 μg/kg (0.02 mg/kg); minimum single dose: 0.5 mg; maximum single dose: 500 μg (0.5 mg) For emergent preintubation bradycardia prophylaxis: 20 μg/kg (0.02 mg/kg) Intubation: No minimum dose; maximum single dose 500 μg (0.5 mg)	Vagal-mediated bradycardia; primary atrioventricular block; emergent intubation bradycardia prophylaxis	Loss of constrictive pupillary reflex to light
Calcium chloride (10% = 100 mg/mL = 27.2 mg/mL elemental calcium)	10–20 mg/kg; maximum single dose: 2 g	Hypocalcemia	Precipitates with sodium bicarbonate; rapid IV administration can cause hypotension, bradycardia, or asystole (particularly if the patient is receiving digoxin)
Calcium gluconate (10% = 100 mg/mL = 9 mg/mL elemental calcium)	50–100 mg/kg; maximum single dose: 3 g	Hypocalcemia	Precipitates with sodium bicarbonate; rapid IV administration can cause hypotension, bradycardia, or asystole (particularly if the patient is receiving digoxin)
Dexmedetomidine	0.5–1 μg/kg bolus; infusion 0.25–1 μg/kg/hour; titrate to effect	For sedation and mild analgesia	If at risk for heart block or symptomatic bradycardia, pacing capability should be available; can cause hypotension or bradycardia
Dobutamine	2–20 μg/kg/min	Myocardial systolic dysfunction (i.e. as inotrope and/or vasodilator)	Titrate to effect; can produce hypotension or tachyarrhythmias

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Table 25.3 (Continued)

Medication	Dose	Indications	Cautions/precautions
Dopamine	2–20 μg/kg/min; if ≥20 μg/kg/min is required, consider using an alternative adrenergic agent	Systolic dysfunction; postoperative LCOS	Titrate to effect; can produce vasoconstriction and hypertension or tachyarrhythmias; increases myocardial oxygen consumption
Epinephrine	For pulseless cardiac arrest: Bolus: 10 μg/kg (0.01 mg/kg, or 0.1 mL/kg of 0.1 mg/mL) concentration during cardiac arrest; maximum dose: 1 mg For symptomatic bradycardia: Bolus: 10 μg/kg (0.01 mg/kg, or 0.1 mL/kg of 0.1 mg/mL) concentration; maximum dose: 1 mg For treatment of hypotension or persistent bradycardia with a pulse in the patient with an at-risk myocardiurnt: Give low dose via central administration 1 μg/kg (0.001 mg/kg); continuous infusion: 0.01–0.2 μg/kg/min[b]	Cardiac arrest; symptomatic bradycardia; systolic dysfunction; postoperative LCOS	Significant vasoconstriction at higher doses; increases myocardial oxygen consumption
Esmolol	Bolus: 100–500 μg/kg (0.1–0.5 mg/kg) over 1–2 minutes Infusion: 50–500 μg/kg/min	SVT; hypertension	Can cause bradycardia, hypotension, and/or hypoglycemia
Etomidate	Bolus: 0.2–0.4 mg/kg, over 30–60 seconds; maximum dose: 20 mg	Procedural sedation	Can cause apnea and adrenal suppression
Fentanyl	Bolus: 1–5 μg/kg continuous infusion for neonates and young infants: 0.5–5 μg/kg/hour Continuous infusion for older infants and children: 1–3 μg/kg/min	Analgesia	Can cause apnea and chest wall rigidity in the naive patient
Furosemide	1 mg/kg; starting dose of up to 10 mg to naive patient	Diuresis	Can cause hypokalemia, hypochloremic metabolic acidosis, or hypotension if preload dependent
Heparin	Presumed shunt occlusion: 50–100 U/kg; anticoagulation before ECLS cannulation: 100 U/kg	Presumed shunt occlusion; ECLS cannulation	Can cause bleeding
Hydrocortisone	1–2 mg/kg; maximum dose: 100 mg	LCOS not responsive to inotropic agents	Can cause hyperglycemia and/or hypokalemia
Isoproterenol	0.05–2 μg/kg/min	Post–cardiac transplantation; long QT with torsade des pointes; primary atrioventricular block	Can cause hypotension, tachycardia, and increased myocardial oxygen consumption
Ketamine	0.5–2 mg/kg	Procedural sedation	Can cause apnea and increased respiratory secretions; myocardial depressant at high doses
Levosimendan	Bolus: 12 μg/kg; infusion: 0.1 μg/kg/min	LCOS	
Lidocaine	Bolus: 1 mg/kg. may repeat Infusion: 20–50 μg/kg/min (repeat bolus dose if infusion initiated >15 minutes after initial bolus dose)	VF/pulseless VT cardiac arrest; ventricular arrhythmias	Monitor QTc and lidocaine levels; can cause seizures at high levels
Magnesium sulfate	Pulseless VT with torsade des pointes; bolus: 25–50 mg/kg; maximum dose: 2 g VT with pulses: 25–50 mg/kg over 10–20 minutes; maximum dose: 2 g	VF/pulseless VT arrest with torsade des pointes; hypomagnesemia	Can cause hypotension with rapid administration
Midazolam	0.05–0.2 mg/kg	Sedation	Can cause apnea or hypotension
Milrinone	Bolus: 50 μg/kg, administered over 10–60 minutes Maintenance infusion: 0.25–1.0 μg/kg/min	LCOS	Hypotension

(*Continued*)

Table 25.3 (Continued)

Medication	Dose	Indications	Cautions/precautions
Nitric oxide	Up to 40 ppm	Increased pulmonary vascular reactivity; pulmonary hypertension ± crisis	Methemoglobinemia
Norepinephrine	Infusion: 0.025–0.3 μg/kg/min	LCOS with low SVR; clinically significant vasodilation	Vasoconstriction; increases myocardial oxygen consumption
Oxygen	FiO_2 = 21–100%	Alveolar desaturation	Pulmonary overcirculation with an unrestrictive aortopulmonary shunt
Phenylephrine	Bolus: 5–20 μg/kg; (0.005–0.020 mg/kg) Infusion: 0.1–0.5 μg/kg/min	Cyanotic spell in unrepaired tetralogy of Fallot; symptomatic hypotension because of low SVR; shunt obstruction; coronary hypoperfusion	Can cause vasoconstriction or hypertension
Propofol	Bolus: 1–3 mg/kg Infusion: 50–100 μg/kg/min	Sedation, amnesia	Hypotension; contraindicated in children with mitochondrial disease and not approved in children for prolonged sedation
Procainamide	Bolus: 15 mg/kg over 30–60 minutes; maximum dose: 100 mg Infusion: 20–60 μg/kg/min	JET; SVT; atrial fibrillation	Monitor ECG and procainamide and NAPA levels; can prolong QT interval: 1. Obtain expert consultation before administering, if known or suspected long QT; 2. Routine administration in combination with amiodarone is not recommended without expert consultation
Prostaglandin E_1	To establish ductal patency: 0.05–0.1 μg/kg/min, IV/IO infusion To maintain ductal patency: 0.01–0.05 to 0.01–0.02 μg/kg/min IV/IO infusion	Maintain patency of ductus arteriosus	Apnea; fever and hypotension
Sodium bicarbonate	Bolus: 1–2 mEq/kg slow IV push; dose adjusted to severity of base deficit; use 4.2% (0.5 mEq/L) concentration for neonates	Metabolic acidosis	Precipitates with calcium
Vasopressin	Infusion: 0.0005–0.01 U/kg/min	LCOS with low SVR; vasodilatory shock; diabetes insipidus	Hypertension and increased afterload; fluid retention
Verapamil	Bolus: 0.1–0.2 mg/kg Do not administer to infants <12 months of age without expert consultation	SVT	Hypotension; have calcium available; not to be administered to infants (can cause apnea, bradycardia, and hypotension); avoid in patients with WPW

Source: Marino et al. [19]. Reproduced with permission from Wolters Kluwer Health, Inc.

ECLS indicates extracorporeal life support; FiO_2, fractional inspired oxygen; IO, intraosseous; IV, intravenous; JET, junctional ectopic tachycardia; LCOS, low cardiac output syndrome; NAPA, *N*-acetylprocainamide; SVR, systemic vascular resistance; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; and WPW, Wolff-Parkinson-White syndrome.

[a] The time range for the administration of the loading dose of amiodarone for the child with a perfusing rhythm is slightly longer (i.e. 30–60 minutes) than the pediatric advanced life support (PALS) 2015 recommended time for administration (i.e. 20–60 minutes). The reason for this slight difference is that the child with cardiac disease is likely to be or is at risk for hemodynamic compromise.

[b] For treatment of hypotension or persistent bradycardia with a pulse in the patient with an at-risk myocardium, give low dose via central administration 1 μg/kg (0.001 mg/kg), which is one-tenth the standard recommended resuscitation dose for symptomatic bradycardia in PALS 2015.

Phases of cardiac arrest

Regardless of the location in which a CA occurs, the provision of high-quality CPR is highly dependent on rapid, coordinated, team-based actions that extend throughout the spectrum of care both before, during, and after hypoxic-ischemic arrest states (no flow/low flow). The likelihood of ROSC, survival to hospital discharge, and neurologic survival are all improved when patients receive high-quality CPR [16]. Measures of high-quality CPR include the provision of chest compressions with appropriate depth, rate, and recoil; minimal interruptions in chest compressions (high chest compression fraction); appropriate ventilation and monitoring of adequacy of ventilation; and reversal of treatable causes. Resuscitation science has historically focused on these elements of CPR including logistics and management

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of chest compressions, assisted ventilation, defibrillation for shockable rhythms, and pharmaceutical reanimation measures. However, recent efforts by the international resuscitation community have extended this focus to include prearrest and postarrest care in light of the reports demonstrating a plateau in survival outcomes for IHCA and OHCA in the pediatric population [21]. Subgroup analyses for outcomes data surrounding anesthesia-related CA for patients with CHD are limited although care processes across the CA spectrum should not be limited by patient or hospital-level factors [19].

In order to emphasize the importance of the elements of pre-/intra-/post-arrest care, the 2020 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care report highlighted the importance of each element of care along the CA spectrum by utilizing the Chains of Survival model (see Figure 25.1).

Prevention of CA in the in-patient and/or peri-anesthetic setting has traditionally been limited to anticipatory management of known high-risk populations such as those with single-ventricle CHD before/after Stage 1 repair, suprasystemic pulmonary hypertension, left-ventricular outflow tract obstruction, and Williams syndrome [5, 22]. Recent quality improvement efforts by the PC4 have involved national implementation of a CA prevention bundle which identified high-risk populations; standardized anticipatory care plan discussions twice a day; and provided ready access to resuscitation medications, sedation for noxious stimulation, and post-arrest debriefing tools. Applying this methodology to the periprocedural environment presents challenges surrounding the predominantly nonmodifiable patient and procedure-based factors that are presenting constant threats during operations and cardiac catheterizations. Ultimately, highly successful specialized teams with specific equipment, knowledge, and resources can rapidly respond to clinical decompensation events in the CHD population with precision and quality.

The 2020 updated algorithm and recommendations for the provision of high-quality CPR are summarized in Figure 25.2. Pediatric CPR is uncommon and thus very challenging to maintain excellent team skills, even in larger tertiary care children's hospitals. Increasingly, high-fidelity chest compression and ventilation data have become available to provide real-time guidance to care teams providing CPR. These CPR feedback devices, when paired with invasive arterial blood pressure and end-tidal CO_2 monitoring, are shifting the paradigm away from provider-focused CPR training, to one that is patient physiology and hemodynamically focused [23]. Measuring these physiological parameters, which are often available to the anesthesiologist during surgical and/or catheterization procedures, can be used to trend CPR quality, guide therapies during CPR, and gauge likely outcomes like ROC. In retrospective fashion, these data also are available in aggregate to guide quality improvement and resuscitation science efforts.

Cardiopulmonary resuscitation that is prolonged and/or resistant to conventional CPR techniques may warrant rescue with mechanical circulatory support should the resources and expertise be available. E-CPR is defined as the deployment and cannulation onto veno-arterial extracorporeal membrane oxygenation (VA ECMO) during active conventional CPR. In the pediatric population, this resource-intense therapy is highly dependent on the complex choreography of resuscitation teams and surgical staff (general/cardiothoracic surgeons) and often utilized in patients with underlying CHD [10]. Historically, E-CPR began as a specific rescue modality after post-cardiotomy cardiac arrest/cardiogenic shock in the pediatric CHD population [24, 25]. It has since evolved beyond the postoperative CHD population to include multiple populations of critically ill children including those with acute fulminant myocarditis, acute decompensated heart failure, and sepsis[10]. Activation of E-CPR teams in the peri-procedural arena may be less cumbersome than CAs occurring in other inpatient or outpatient settings; yet, excellent communication, multidisciplinary training, and resource allocation for perfusion/priming teams are crucial for effective E-CPR in the current era [26].

Post-cardiac arrest care

Achieving ROSC with the resolution of no-flow or low-flow hemodynamic states has historically been the goal of providers during the high-stress environment of a CA. However, since 2008, the international resuscitation community has recognized the role of ischemia-reperfusion injury in the evolution of the disease state known as postcardiac arrest syndrome (PCAS) [27]. Also recognized in the pediatric population, PCAS is composed of several key pathophysiologic components: post-CA brain injury, post-CA myocardial dysfunction, systemic ischemia-reperfusion response, and persistent precipitating pathophysiology [28]. Although a review of the unique pathophysiology of each phase is beyond the scope of this chapter, it is crucial for the cardiac anesthesiologist to consider the post-return of circulation (ROC) management of the patient with CHD who has suffered a CA as a crucial and equally important time period as active CPR. Figure 25.3 (reproduced with permission from Topjian et al. [19]) provides a standardized approach to help clinicians monitor for ongoing secondary organ injury while also providing them with therapeutic options to address the known pathophysiologic derangements, ultimately providing the best opportunity to mitigate brain and other organ injury post-arrest. Excellent overviews of postarrest stabilization can be found in the AHA guidelines [29], and a more recent AHA Scientific Statement [19].

Neurologic monitoring and targeted neuroprotective management

The central nervous system is especially sensitive to hypoxic insult and reperfusion injury, and even with expeditious initiation of CPR, ischemic neuronal cell death rapidly occurs. Furthermore, there is a clear time-weighted burden; with prolonged low-flow states, irreversible injury is inevitable, and beyond 10–20 minutes, the likelihood of neurologically intact survival is low [30]. Neurologic management after CA, therefore, is focused on identifying actionable lesions, reducing cerebral metabolic demand, and optimizing both global and cerebral oxygen delivery.

Postarrest neurologic prognostication is challenged by conflicting evidence and lack of specific biomarkers with high predictive value. Diagnostic neuronal injury patterns

Components of Post–Cardiac Arrest Care	Check
Oxygenation and ventilation	
Measure oxygenation and target normoxemia 94%-99% (or child's normal/appropriate oxygen saturation).	☐
Measure and target $Paco_2$ appropriate to the patient's underlying condition and limit exposure to severe hypercapnia or hypocapnia.	☐
Hemodynamic monitoring	
Set specific hemodynamic goals during post–cardiac arrest care and review daily.	☐
Monitor with cardiac telemetry.	☐
Monitor arterial blood pressure.	☐
Monitor serum lactate, urine output, and central venous oxygen saturation to help guide therapies.	☐
Use parenteral fluid bolus with or without inotropes or vasopressors to maintain a systolic blood pressure greater than the fifth percentile for age and sex.	☐
Targeted temperature management (TTM)	
Measure and continuously monitor core temperature.	☐
Prevent and treat fever immediately after arrest and during rewarming.	☐
If patient is comatose apply TTM (32°C–34°C) followed by (36°C–37.5°C) or only TTM (36°C–37.5°C).	☐
Prevent shivering.	☐
Monitor blood pressure and treat hypotension during rewarming.	☐
Neuromonitoring	
If patient has encephalopathy and resources are available, monitor with continuous electroencephalogram.	☐
Treat seizures.	☐
Consider early brain imaging to diagnose treatable causes of cardiac arrest.	☐
Electrolytes and glucose	
Measure blood glucose and avoid hypoglycemia.	☐
Maintain electrolytes within normal ranges to avoid possible life-threatening arrhythmias.	☐
Sedation	
Treat with sedatives and anxiolytics.	☐
Prognosis	
Always consider multiple modalities (clinical and other) over any single predictive factor.	☐
Remember that assessments may be modified by TTM or induced hypothermia.	☐
Consider electroencephalogram in conjunction with other factors within the first 7 days after cardiac arrest.	☐
Consider neuroimaging such as magnetic resonance imaging during the first 7 days.	☐

Figure 25.3 Post-cardiac arrest care checklist. Source: Topjian et al. [16]. Reproduced with permission from Wolters Kluwer Health, Inc.

may take time to develop, highlighting the general recommendation to avoid neuroimaging for the first 72 hours post-arrest. However, it is sometimes reasonable to pursue early neuroimaging to characterize the extent of injury, and screen for pathology amenable to medical or surgical intervention, such as space-occupying hemorrhage or cerebral edema indicating possible intracranial hypertension. In neonates with open fontanelle, this can be initially performed with cranial ultrasound, but in most children, the initial modality of choice will be head computed tomography (CT). It should be noted that while certain findings (e.g., loss of grey-white differentiation, sulcal effacement, and reversal sign) are unambiguously associated with poor outcome [31], the negative predictive value of a normal scan for survival is only

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68% [32]. Ultimately, the most informative prognostic data is obtained from brain magnetic resonance imaging (MRI), which can detect the extent and location of injury patterns, specifically the watershed ischemia/infarct that correlates with poor outcomes [33]. The anesthesiologist will often be called upon to transport and provide supportive care to these patients for imaging studies as well as for potentially urgent/emergent neurosurgical intervention; hence, it is essential to understand the principles of neuroprotective management.

Neurologic monitoring is often imprecise and nonspecific, but it can afford the clinician useful data upon which to direct therapy. Electroencephalography (EEG), typically a continuous protocol with video monitoring, has become standard of care in the postarrest phase of intensive care unit (ICU) management. Since as many as half of therapeutically cooled post-arrest patients will have seizures, most of which are subclinical/nonconvulsive [34], EEG serves an essential ongoing surveillance function. As seizures impose a substantial metabolic burden on an already vulnerable brain and are independently associated with mortality, it is critical to identify and treat them to mitigate secondary injury. Near-infrared spectroscopy (NIRS) may be used to assess the adequacy of regional blood flow by providing trend data on brain tissue oxygen saturation, a surrogate for oxygen extraction. Monitoring indicators of flow, as opposed to pressure, is crucial after brain injury. Animal data from an experimental swine model has shown that the autoregulatory capacity of the cerebral vasculature, as assessed by NIRS-derived indices, can be significantly altered following CA [35]. While various cerebral oxygenation saturation threshold targets have been proposed, unique caveats exist in the interpretation of NIRS values in children with CHD [36], as they must be considered in the context of the expected appropriate systemic arterial saturation unique to their specific underlying or palliated physiology (i.e. single ventricle anatomy with systemic to pulmonary artery shunts, cavopulmonary anastomoses, or mixing lesions, among others). Similar to the above is the selection of targets for oxygenation and ventilation, which must often be individualized to cardiac physiology. While hypoxemia is clearly detrimental, hyperoxia may also be deleterious in patients at risk for pulmonary overcirculation with an attendant decline in systemic and brain perfusion. Additionally, despite the cerebral vasodilatory effects of hypercapnia, normocapnia should be the default ventilation target for most patients [28].

In addition to diagnosing and treating nonconvulsive status epilepticus, and optimizing cerebral oxygen delivery, postarrest care is also focused on reducing cerebral metabolic demand through targeted temperature management. Fever/hyperthermia is commonly observed after CA, and aggressive control of fever and maintenance of normothermia with pharmacologic and/or mechanical measures is indicated. While improved seizure control has been shown with therapeutic hypothermia [37], there is equipoise on the superiority of directed therapeutic hypothermia on outcomes, with conflicting evidence from a recent large trial [38]. At present, the best evidence for comatose patients suggests either 5 days of strict normothermia, or alternatively, a 48-hour period of 32–34 °C hypothermia, followed by 72 hours of normothermia [39].

Management of postarrest myocardial dysfunction

Like the brain, the myocardium is vulnerable to ischemia-reperfusion injury, and both the precipitating CA as well as the therapies used during resuscitation can lead to significant ongoing ventricular systolic and diastolic dysfunction [40]. While catecholamines serve a critical role in augmenting coronary perfusion pressure, thereby directly improving the success of resuscitation, their vasopressor effects impose an increased afterload and can lead to myocardial oxygen supply:demand mismatch. Accordingly, excessive attention to inappropriately chosen blood pressure targets may not only lead to excessive or inappropriate resuscitation but also perpetuate ongoing myocardial dysfunction. Advanced hemodynamic monitoring technologies allow the clinician to measure and trend in real-time more relevant physiologic data on global and regional blood flow, essential to optimal post-arrest care. While the choice of inotropic, vasopressor, or vasodilator agent is often institution- and provider-dependent, the most appropriate selection can and should be made based on objective and serial hemodynamic assessments. Using such modalities as NIRS, various invasive continuous cardiac output devices [41] and emerging integrative oxygen delivery platforms with predictive analytics [42] can facilitate a more individualized approach and provide early identification of response to therapy and of patients at risk for deterioration (See Chapter 21 for additional discussion of hemodynamic support and monitoring).

Despite appropriate and timely goal-directed and physiologically driven medical hemodynamic support, some patients postarrest will evidence severe and persistent ventricular dysfunction. In this population, veno-arterial extracorporeal membrane oxygenation (ECMO), either as a bridge to recovery or to more durable long-term mechanical circulatory support (MCS) such as ventricular assist device (VAD) can be considered. The selection criteria, indications, technical/surgical aspects, and management of the various devices are beyond the scope of this chapter though they are addressed elsewhere in this textbook (See Chapter 37 for a detailed discussion of mechanical support). For a complete discussion of pediatric MCS, the reader is referred to two excellent recent reviews [43, 44]. Some fundamentals, however, warrant mention. First, and germane to the care of patients with CHD, is an understanding of the unique anatomic or physiologic features imposed by the underlying lesion that have implications on cannulation approach, type of device, and degree of support required (i.e. single or biventricular anatomy, among others) [45]. Second, the provision of such resource-intensive rescue modalities must be reserved for patients with both a reversible cause of arrest and a reasonable probability of favorable neurologic recovery. As mentioned above, this is often a difficult or impossible assessment to make acutely, but there are instances where such support would clearly be futile. Finally, these therapies require significant multidisciplinary, institutional expertise to achieve excellent outcomes [46].

Management of acute kidney injury

The kidneys are also vulnerable to ischemia during different arrest states. Acute kidney injury (AKI), defined and staged by the Kidney Disease: Improving Global Outcomes

(KDIGO) criteria based on creatinine and urine output parameters [47], can manifest following successful resuscitation and is independently associated with mortality [48]. Since early diagnosis may improve outcomes, the identification of predictive biomarkers is an area of active investigation. Urinary neutrophil gelatinase-associated lipocalin (NGAL) has been shown in post-cardiopulmonary bypass patients to predict the development of AKI in children and precede creatinine elevation [49], which may be unreliable during dynamic changes in renal function. This and other biomarkers may serve a similar diagnostic or prognostic role after pediatric cardiac arrest, but no conclusive evidence exists currently. There is no specific treatment for AKI; therapies are largely supportive and are aimed at maintaining overall cardiac output and adequate renal perfusion, avoiding fluid overload, and minimizing further secondary renal insult from nephrotoxic drugs. Continuous renal replacement therapy (CRRT) can be initiated whenever the solute and water excretion or acid-base balance functions of the kidneys become insufficient. The presence of an extracorporeal circuit such as ECMO often allows the hemofilter to be placed as an in-line shunt, facilitating immediate therapy when clinically indicated [50]; however, most other patients will require placement of a short-term hemodialysis catheter. Once initiated, the patient's metabolic status can be tightly controlled, and optimal fluid balance targeted precisely.

Outcomes, prognosis, and follow-up after cardiac arrest

Several large cohort studies of pediatric CA have examined survival as well as midterm neurodevelopmental outcomes in survivors [11, 21, 51]. In general, cardiac surgical patients fare better than medical patients, and those with biventricular anatomy have better outcomes than those with single ventricle anatomy. Amongst pediatric survivors of IHCA following cardiac surgery, 5-year survival has been reported as high as 66%, however, with demonstrably worse neurologic outcomes than age- and surgical risk-matched controls. This study also found a linear correlation between both time-to-CPR initiation and total CPR duration and outcome [52].

Irreversible injury to the myocardium and kidneys can be managed with mechanical support or dialysis, respectively, and ultimately transplantation if not otherwise contraindicated. Children who suffer catastrophic brain injury following CA, conversely, cannot be salvaged in a similar manner for obvious reasons. Families of these children rightly wish for frank and evidence-informed prognostication to assist them in making difficult decisions around the maintenance or cessation of life-sustaining therapies. While neuroimaging has notable shortcomings in this regard, there is emerging interest in identifying serum brain-specific biomarkers that may predict the outcome. Serum neuron-specific enolase (NSE), S100b, and myelin basic protein (MBP) are specific to neurons, astrocytes, and myelin, respectively, and have been shown to correlate with mortality and functional neurologic outcome as assessed by the Pediatric Cerebral Performance Category scale [53, 54]. While these markers are not in widespread clinical practice, they may provide clinicians predictive data to guide discussions with families as well as to identify at-risk patients whose clinical assessment may be obfuscated by neuroactive medication, critical illness, or equivocal imaging findings.

Survivors of pediatric cardiac arrest clearly are at risk of severe, permanent, and debilitating adverse neurodevelopmental outcomes. As such, many will need ongoing intensive neurorehabilitation care, and ultimately be rendered technology-dependent. There are both immediate peri-arrest and long-term ethical considerations that this raises, and the defensible choice is not always congruent with the wishes of the family or even the entirety of the medical team. The complex medical and legal factors implicit in this will not be discussed here, but all providers of care to these children must be cognizant of this and strive to treat them and their families with compassion.

KEY POINTS: POST CARDIAC ARREST CARE

- Post-CA syndrome, which results from ischemia-reperfusion injury during CPR, is characterized by brain injury, myocardial dysfunction, and renal insufficiency. It may influence mortality from arrest and must be managed as expertly as CPR itself.
- Neuroprotective care after CPR should include diagnosis and management of seizures, optimization of cerebral oxygen delivery, and reduction of cerebral metabolic demand.
- Treatment of myocardial dysfunction should be individualized via advanced physiologic and hemodynamic monitoring to avoid myocardial oxygen supply: demand mismatch.
- Outcomes from resuscitation are better in children after cardiac surgery versus medical admission, and children with biventricular hearts compared to single ventricle anatomy.

Cardiopulmonary resuscitation for the congenital heart disease patient

While CPR outcomes have improved in recent years, it remains true that conventional CPR techniques have not advanced to provide more than half of normal cardiac output during an arrest [55]. Therefore, CPR avoidance via astute pre-arrest management represents the best strategy for care of infants and children with CHD. However, cardiac patients are more prone to arrest [56, 57], and the pathogenesis of their events may be greatly influenced by their individual anatomy and physiology. Three functional conditions that limit the effectiveness of conventional CPR in cardiac patients are (i) limitation to stroke volume (for example, with atrioventricular valve regurgitation, left ventricular outflow tract obstruction, or low ventricular diastolic volume with restrictive myocardial physiology), (ii) limitation of pulmonary blood flow and oxygenation (with pulmonary valve/pulmonary arterial stenosis or pulmonary artery hypertension, or cavo-pulmonary connection wherein superior vena cava flow is reduced), and (iii) limitation of arterial perfusion to

cerebral or coronary vasculature (e.g. semilunar valve regurgitation or aorto-pulmonary runoff, and/or low "diastolic" blood pressure (BP) during chest compression relaxation with poor coronary perfusion pressure) [58]. The response of heart patients to pharmacological interventions such as epinephrine may also vary by lesion, the degree of heart failure, or preoperative or postoperative condition.

Once an arrest has occurred, emphasis upon the performance of high-quality CPR – to include the provision of adequate chest compression rate and depth, minimization of interruptions in CPR, allowance for full chest recoil between compressions, and avoidance of excessive ventilation - is paramount, just as in the noncardiac population [59]. Use of adjunctive CPR techniques that ameliorate physiologic difficulties with CPR in the cardiac population, such as interposed abdominal compression CPR (IAC-CPR), may be considered [see sections below]. Those failing to achieve sustained ROSC in specialized cardiac ICU environments should be placed on extracorporeal life support if the arrest etiology is potentially reversible or as a bridge to alternate therapy (usually durable mechanical circulatory support or heart transplantation).

Some lesion-specific measures for arrest avoidance are mentioned in the sections below as well as considerations unique to the performance of CPR in that population.

Left-heart lesions

Mitral valve disease

Isolated mitral stenosis is uncommon in children and most often occurs in combination with additional left-sided obstructive lesions or Shone's complex (aortic coarctation, subaortic and/or aortic stenosis, and supra-mitral ring or a dysplastic, parachute mitral valve) [60]. The poorly developed mitral valve may also be regurgitant. Whether through stenosis or regurgitation, high left atrial pressures may be present resulting in pulmonary edema, pulmonary venous hypertension, and reactive pulmonary artery hypertension (PAH). Over time, muscularization of pulmonary veins may progress causing pulmonary vascular resistance (PVR) to rise, further exacerbating PAH. Management of these patients prior to surgical intervention should entail avoidance of fluid overload, especially in the setting of left ventricle (LV) systolic or diastolic dysfunction, eschewing rapid administration of large volume boluses that might worsen left atrial hypertension (with mitral stenosis) or distend the mitral annulus and LV, worsening mitral regurgitation or elevating LV end-diastolic pressure. Postoperatively, left atrial pressure should be monitored in addition to central venous pressure (CVP) to provide insight into hemodynamic derangements. Low left atrial pressure either represents hypovolemia (with low CVP) or elevated PVR (with high CVP). High left atrial pressure may indicate volume overload (with high CVP), residual mitral disease, or ventricular dysfunction irrespective of etiology. Withdrawal of several milliliters of blood in neonates may temporarily relieve left atrial hypertension from volume overload. Low cardiac output must be avoided using inotropic support and afterload reduction. Milrinone (an inotrope, vasodilator, and lusitrope) and mechanical ventilation with positive pressure (which lowers LV afterload) may both be useful.

Resuscitation of patients with mitral valve stenosis should proceed according to standard algorithms, although blood flows could be compromised by the limitation of preload to the left heart during chest compressions. High PVR and left atrial hypertension limit pulmonary blood flow (PBF), and mitral stenosis limits inflow to the LV. CPR patients with mitral regurgitation suffer from the inefficiency of regurgitant flow across the mitral valve that reduces cardiac output with each chest compression. Lack of response to early resuscitative efforts should prompt consideration of extracorporeal support.

Aortic valve disease

Aortic stenosis may be seen in isolation or as part of the aforementioned Shone's complex. Left ventricular hypoplasia may also be present in more severe forms of this constellation, along with associated endocardial fibroelastosis indicative of subendocardial ischemia. These patients are at risk for left atrial hypertension (from poor ventricular compliance) and pulmonary edema formation. Assessment of the adequacy of left-sided structures for two-ventricle circulation becomes paramount. Intracardiac exploration of the mitral valve (opening <8 mm and an abnormal subvalvular apparatus) may suggest the need for single ventricle palliation [61] and the use of echocardiographic mitral and aortic Z-scores [62] aid surgical decision-making. Those who are likely to support a biventricular circulation may undergo either percutaneous balloon aortic valvuloplasty or surgical valvuloplasty, often with significant improvement in cardiac function [63]. Newborns with critical aortic stenosis require prostaglandin to maintain ductal patency for blood flow to the systemic circulation. They commonly present with LV dysfunction, with either a hypertrophied or dilated LV. These patients may remain unstable after their procedure and require inotropic support and/or afterload reduction. Prostaglandin should be weaned off and adequacy of circulation assessed.

Children with aortic valve regurgitation suffer from volume loading of the ventricle, which results in remodeling and progressive LV dilation and dysfunction. The occurrence of low diastolic BP may cause coronary insufficiency and myocardial ischemia, which further compromise LV function. Aortic valve repair or replacement becomes necessary with increasing severity of symptoms and LV dilation.

As with all cardiac patients who require resuscitation, high-quality CPR is the mainstay of therapy. However, patients with aortic stenosis face the challenge of reduced stroke volume with chest compressions owing to obstruction to LV outflow. This compromise in cardiac output may worsen coronary perfusion to a hypertrophied myocardium resulting in ischemia. Moreover, a hypertrophied LV with poor compliance will fill poorly during CPR, which will also reduce stroke volume and cardiac output. Thus, the aortic stenosis population may contend with both poor filling and poor output during resuscitation. Not surprisingly, aortic stenosis has been found in adults to be a strong independent predictor of mortality and poor outcome after IHCA [64]. Patients with aortic insufficiency may experience limited cardiac output from chest compressions due to regurgitation of flow back into the LV. Low "diastolic" BP during chest

recoil may also compromise coronary perfusion pressure. E-CPR may be necessary if conventional techniques prove inadequate.

Right-heart lesions

Patients with right ventricular (RV) outflow obstruction (for example, tetralogy of Fallot, double outlet RV with pulmonic stenosis, or pulmonic stenosis) and/or small right-sided structures typically have varying degrees of pressure overload and resultant RV hypertrophy, which may necessitate outflow tract intervention. Ventriculotomy and muscle resection may affect systolic and diastolic ventricular performance, while postoperative pulmonary insufficiency (made worse by elevation in post-bypass PVR) may represent an acute volume load. RV workload may also be increased by elimination of lower resistance outlets for flow, such as the closure of ventricular septal defects or tricuspid valve repairs which limit regurgitation. In this setting, RV function may be further harmed by positive pressure ventilation with elevated mean airway pressure, resulting in increased RV afterload. Loss of sinus rhythm with atrioventricular dyssynchrony may compromise the atrial contribution to ventricular filling and cause low cardiac output.

Once RV diastolic function deteriorates sufficiently, the RV may almost serve as a passive conduit in which there is persistent diastolic prograde flow into the pulmonary artery with atrial contraction. This is termed restrictive RV physiology. Systemic venous pressure becomes elevated with the increase in RV end-diastolic pressure, which can lead to capillary leak, pleural and peritoneal fluid accumulation, renal insufficiency from abdominal compartment syndrome, and later feeding intolerance and chylous effusions. Drainage of the pleural compartment may avoid counterproductive increases in ventilator settings, and peritoneal catheter placement may avoid impairment of inferior vena cava flow. Having a peritoneal catheter in place could also facilitate dialysis with beneficial inflammatory mediator removal [65]. It is important to recognize that poor RV compliance may diminish RV preload and thus LV preload. An atrial level right-to-left shunt may ameliorate the situation by preserving LV preload and systemic output at the expense of systemic arterial saturation.

Treatment of the failing RV should be directed toward ventilator management that minimizes PVR, thus avoiding the extremes of hyperinflation and atelectasis, along with consideration of use of inhaled nitric oxide and early extubation (latter may be good for RV output, but this must be balanced against the potentially detrimental effects of respiratory distress and loss of airway patency). Secondly, the maintenance of adequate intravascular volume for RV filling is necessary. Third, the maintenance of AV synchrony is paramount, and this may entail atrial or AV sequential pacing or dysrhythmia management. Fourth, judicious use of inotropic support (such as low-dose epinephrine and vasopressin) to preserve systolic and diastolic BP may be warranted. Titration of milrinone should be considered if blood pressures are sufficient. Lastly, heart rate control to optimize diastolic filling time should be considered. This may entail the use of adequate sedation and analgesia (i.e. dexmedetomidine) and early use of low dose esmolol infusion in patients not requiring ß-agonist support.

Resuscitation of children with right-sided outflow obstruction may be complicated by the limitation of PBF, resulting in poor LV preload and poor cardiac output. Even the repaired RV outflow tract may be compromised by chest compressions; hence, correct hand position on the lower half of the sternum should be utilized [59]. Patients with significant RV diastolic dysfunction may require fluid during CPR to achieve adequate ventricular filling, and full chest recoil should be employed to refill the thoracic compartment and right heart during CPR diastole. In the future, adjunctive measures to improve venous return to the right heart, such as IAC-CPR or perhaps the impedance threshold device, may prove beneficial (see section below).

Total anomalous pulmonary venous connection

Total anomalous pulmonary venous connection (TAPVC) routes pulmonary venous blood to the right atrium resulting in dilated right-sided chambers and small left-sided structures. Whether supracardiac, cardiac, mixed-type, or infracardiac, there is always some degree of obstruction experienced to venous return in comparison to normal pulmonary venous architecture. Severe obstruction may present in the newborn period and may be difficult to distinguish from neonatal pulmonary disease. Therefore, newborns on ECMO should be carefully evaluated for TAPVC. Presentation with pulmonary venous congestion, interstitial edema, and elevated RV pressure is a characteristic that may be associated with labile pulmonary hypertension. Preoperative management is complicated by the fact that prostaglandin for ductal patency and pulmonary vasodilators given to enhance oxygenation may worsen pulmonary edema. Surgical intervention is indicated, though the postoperative period may be difficult due to the small size and poor compliance of the chronically underfilled LV, presence of pulmonary hypertension, and respiratory failure. Pulmonary vasodilators in the form of oxygen, inhaled nitric oxide, and milrinone may be helpful postoperatively. Deterioration late in the convalescent period should warrant investigation for recrudescent pulmonary hypertension.

TAPVC patients who experience arrest should be treated for reversible causes of elevated PVR (e.g., arrhythmia, unintended interruption of vasodilator therapy, acidosis, hypoxia, hypercarbia, agitation) as well as common postoperative complications such as cardiac tamponade, accidental extubation, and others. High-quality CPR may not generate adequate pulmonary blood flow due to high PVR, which may further compromise LV filling and cardiac output. Use of 100% oxygen, inhaled nitric oxide, and volume for LV preload is warranted. Despite these interventions, ECPR may be required.

Single ventricle lesions

Single ventricle physiology is characterized by the complete mixing of systemic and pulmonary venous return resulting in equal pulmonary and systemic arterial saturations. Total ventricular output (the sum of pulmonary blood flow, systemic blood flow, and atrioventricular regurgitant volume) is divided between parallel pulmonary and systemic circuits based upon relative pulmonary (PVR) and systemic (SVR) resistances. This inherently inefficient situation represents a

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significant burden for the volume-loaded single ventricle, and surgery in the newborn period is often required for palliation. The goals of initial (Stage 1) palliation are as follows: (i) to open the atrial septum to allow egress of blood from the pulmonary venous atrium, (ii) to create an unobstructed path for systemic output, and (iii) to establish a stable, controlled source of pulmonary blood flow (either a modified Blalock-Taussig-Thomas (BTT) shunt or an RV to pulmonary artery "Sano" shunt).

Postoperative management after Stage 1 palliation is directed toward assurance of adequate oxygen delivery and cardiac output. This is assessed via estimates of the systemic venous oxygen saturation (using cerebral near-infrared spectroscopy as a surrogate for superior vena cava saturation) and the arteriovenous saturation difference (using arterial pulse oximetry), and tracking of serum lactates. Clinical assessment of patient heart rate, BP, perfusion, urine output, and feeding tolerance, when applicable, are also critical. The ratio of pulmonary to systemic blood flow (which is subject to inaccuracies related to the estimation of pulmonary venous oxygen saturation) may also be determined to understand the balance between parallel circulations, with a goal ratio slightly below or near unity. Low cardiac output may manifest with decreased arterial saturation. As oxygen delivery worsens, an increased sympathetic tone may preserve systolic BP, and arterial runoff may preserve the ability to palpate pulses. However, low diastolic BP, high intracardiac filling pressures, and higher HR will lower coronary perfusion pressure and diastolic filling time and together may result in coronary ischemia. In the setting of low cardiac output, one must also be suspicious of residual lesions, particularly residual aortic obstruction or compromised coronary artery anatomy. These may be evaluated expeditiously by echocardiography and ECG. Hemodynamic compromise may often be reversed through manipulation of preload (volume or blood transfusion), inotropic support, mechanical ventilation (change in PVR), and titration of oxygen to optimize near-infrared spectroscopy, or sedation/analgesia and afterload reduction (change in SVR).

It is known that arrest rates are high in the SV population due to the volume load on the single RV (especially if there is significant AV valve regurgitation), the imbalance between pulmonary and systemic blood flows, and the risk of shunt thrombosis [19] [66]. Survival may be influenced by anatomic variant (Hypoplastic left heart syndrome (HLHS), TAPVC, and pulmonary atresia/intact ventricular septum with RV-dependent coronary circulation), significant semilunar or atrioventricular valve regurgitation, decreased single ventricle function, and comorbidities including prematurity and genetic syndromes [19] [67]. High-quality conventional CPR is recommended in cardiac arrest, but this raises intrathoracic pressure during the compression cycle and may limit PBF. Low "diastolic" pressure during chest decompression may also reduce the driving pressure for PBF in the case of the modified BTT shunt, and low SVR may limit PBF in the Sano population. Thus, both groups may experience poor blood oxygenation as CPR progresses, with low systemic oxygen content. Hypoxemia coupled with poor coronary perfusion pressure from low diastolic BP and high filling pressures results in coronary ischemia. Not surprisingly, prolonged CPR is associated with worsened outcomes [68]. Shunt or stent compression during CPR is also possible [69] [70]. Change in hand position to the lower 25% of the sternum [71], hemodynamically targeted CPR to maintain diastolic BP above a designated threshold [72], or adjunctive interventions such as sternal reopening (early after surgery) or interposed abdominal compression may be considered. E-CPR activation should be undertaken early. Once the decision is made to initiate extracorporeal circulatory support, repeated doses of epinephrine and vasopressin should be limited due to their persistent afterload effects upon a weakened myocardium.

Superior cavo-pulmonary connection (bidirectional Glenn, or stage 2 palliation)

At approximately 3–6 months, the second stage of single ventricle palliation is undertaken which involves anastomosis of the superior vena cava (SVC) to the pulmonary artery. Postoperatively, these patients benefit hemodynamically from early extubation because of the negative intrathoracic pressure generated by spontaneous respiration. This augments cerebral venous return to the SVC, effective pulmonary blood flow, preload to the systemic ventricle and cardiac output. For those who require mechanical ventilation, hypoventilation with mild hypercapnia will decrease cerebral vascular resistance and augment cerebral blood flow more than hyperventilation and alkalosis augment PBF. Thus, hyperventilation impairs oxygenation despite a decrease in transpulmonary gradient [73] [74]. Patients who manifest desaturation after the superior cavo-pulmonary anastomosis should be evaluated for anatomic causes of reduced PBF such as veno-venous collaterals from the SVC to the pulmonary veins or inferior vena cava, pulmonary artery stenosis, or pulmonary arteriovenous malformations. Thought should also be given to the presence of ventricular dysfunction, atrioventricular valve regurgitation, arrhythmia with loss of atrioventricular synchrony, and pulmonary issues such as hemi-diaphragmatic paralysis and atelectasis/infiltrate. Prior to the arrest, and in the presence of preserved lung function, one may consider a paracorporeal support system with atrial and aortic cannulation, and use of a centrifugal pump [75].

The response to conventional CPR in superior cavo-pulmonary connection cardiac arrest is poor [19]. This may related to the diminution of cerebral blood flow that occurs with chest compressions and raised intrathoracic pressure (creating risk for neurologic injury), as well as the decrease in PBF that results downstream from the cerebral vasculature. Reduced PBF leads to a reduction in systemic ventricular preload and cardiac output. Atrio-ventricular valve regurgitation or semilunar valve regurgitation may worsen cardiac output as well. Chest recoil during CPR becomes critical to allow for venous inflow to the lungs. The use of a CPR adjunct such as IAC-CPR may hold future benefits through augmentation of cerebral blood flow, though this theory is untested at the present time. Results from ECPR in this population are challenged by difficulties with the site of venous cannulation to effectively decompress the heart and the Glenn circuit. If PVR remains low, it may be possible to support cardiac output via the inferior vena cava and aortic cannulation, while allowing superior vena cava flow to continue through the lungs for oxygenation.

Complete superior-inferior cavo-pulmonary connection (Fontan, stage 3 palliation)

This operation is typically accomplished between 2 and 4 years of age, with baffling of all systemic venous return to the pulmonary arteries. This requires passive flow through the lungs of all systemic ventricular preload. Thus, cardiac output is highly dependent upon low PVR and adequate ventricular function. Accordingly, Fontan patients benefit hemodynamically from early extubation postoperatively, but if mechanical ventilation is required, mean airway pressures should be minimized. Fenestration of the Fontan circuit (i.e. connection between the Fontan conduit and the atrium) may maintain ventricular preload at the expense of arterial saturation in the setting of elevated PVR. Non-fenestrated patients with high PVR will appear highly saturated with evidence of poor perfusion and low output. Use of vasopressin preferentially for BP augmentation (due to its greater effect upon SVR than PVR), and for early postoperative venoconstriction to reduce the formation of effusions has been adopted in some centers [76].

Survival from CA in Fontan patients mirrors that in superior cavo-pulmonary connection patients. Evaluation of the Society of Thoracic Surgeons database revealed a Fontan arrest mortality rate of 41.2% [77]. Resuscitative efforts are challenged by the fact that chest compressions reduce PBF, and limit oxygenation and preload to the systemic ventricle. Elevations in SVC pressure limit cerebral blood flow, again making chest recoil important to resuscitation physiology. Early institution of ECPR as a potential bridge to mechanical circulatory support or heart transplantation may provide a useful salvage pathway. Tables 25.4 and 25.5 display the resuscitation profiles at the three stages of single ventricle surgical palliation, and the effect of respiratory manipulations on circulatory parameters at the three stages of palliation.

Anomalous coronary syndromes

Anomalous aortic origin of a coronary artery (AAOCA) is a rare congenital abnormality of the origin or course of an aberrant coronary artery, with both arising from the same aortic sinus of Valsalva, via either a single or dual ostia. The anomalous vessel can be either the right or left coronary, and exists on a wide spectrum, taking intraarterial, intramural, or intraconal/intraseptal courses. Disease severity seems to relate in part to this anatomic coursing, with intraarterial variants posing the most risk. AAOCA is the second leading cause of sudden cardiac death (SCD) in young athletes and has a prevalence range estimated between 0.1 and 1% of the population by large angiography database studies, and with a 3 : 1 male predominance [78]. As this disease is often clinically silent with the first presentation being sudden arrest during exercise, the initial arrest often occurs out of the hospital. While the genetic basis of AAOCA is not elucidated, there may be a familial inheritance, with clusters of sudden cardiac arrest (SCA) occurring in first-degree relatives [79].

The mechanism of ischemia and SCD is hypothetical but thought to be due to ostial stenosis, vasospasm, and intramural compression between the great vessels, as well as a proarrhythmogenic process, either induced by ischemia or via a secondary mechanism triggering lethal arrhythmias. The AAOLCA variant, where the LCA takes its origin from the right sinus, seems to be a higher-risk lesion, with a 6% 20-year mortality risk amongst children and young adults [80].

Table 25.4 Resuscitation profiles for the structurally normal heart and those who have undergone single-ventricle palliation

Physiology	Circulation description	Circulation of blood	Chest compressions	Chest recoil	Positive-pressure ventilation
Structurally normal heart	Two-ventricle series circulation without heart disease	Systemic veins – lungs – pulmonary veins – body	1. RV compression results in PBF 2. LV compression results in SBF	Increases the transthoracic gradient from the systemic veins to the RA, increasing RV filling	Decreases the transthoracic gradient from the systemic veins to the RA, decreasing RV filling
Stage 1 Norwood or shunted physiology	Single-ventricle parallel circulation with shunt-dependent PBF	Systemic veins – single ventricle – lungs (via shunt) or body	Single-ventricle compression results in PBF (shunt ± PVR) and SBF (SVR)	Increases filling to the preload-dependent single ventricle	Decreases filling to the preload-dependent single ventricle
Bidirectional Glenn and hemi-Fontan	Single-ventricle parallel circulation with PBF dependent on multiple arteriolar vascular beds	IVC – single ventricle – body/brain – SVC – lungs – pulmonary veins – body	Single-ventricle compression results in SBF	1. Predominantly fills the RA from the IVC 2. SVC flow dependent on cerebral vascular resistance and PVR	Decreases filling to the single ventricle by impeding SVC flow and IVC filling
Fontan	Single-ventricle series circulation	Systemic veins – lungs – pulmonary veins – body	Single-ventricle compression results in SBF	1. Predominantly fills the PAs with IVC blood flow (PVR) 2. SVC flow dependent on cerebral vascular resistance and PVR	Decreases filling to the single ventricle by impeding both SVC and IVC flow

Source: Marino et al. [19]. Reproduced with permission from Wolters Kluwer Health, Inc.

IVC indicates inferior vena cava; LV, left ventricle; PA, pulmonary artery; PBF, pulmonary blood flow; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; SBF, systemic blood flow; SVC, superior vena cava; and SVR, systemic vascular resistance.

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Table 25.5 Effect of respiratory manipulations on circulatory parameters at different stages of palliation of children with univentricular physiology

Stage and respiratory strategy (alveolar gas)	SaO_2	SvO_2	Q_p/Q_s	TPG	AVO_2D	VO_2	Lactate	CBF	rSO_2C	rSO_2S
0										
Hypocapnic										
Hyperoxic										
Hypercapnic[56, 59]	↑	↑	↓		↓				↑	
Hypoxic[56, 59]	↓	↓	↓		↔				↔	
1										
Hypocapnic[97]	↔	↔			↔					
Hyperoxic[97]	↑	↑			↔					
Hypercapnic[60, 94]	↔	↔↑	↔		↓	↓	↓	↑	↑	↓
Hypoxic										
2										
Hypocapnic[58]	↓				↔				↓	
Hyperoxic[93]	↑									
Hypercapnic[58, 91–94]	↑↑		↔	↑	↓	↓	↓	↑	↑	
Hypoxic										

Source: Marino et al. [19]. Reproduced with permission from Wolters Kluwer Health, Inc.

Measured parameters in multiple studies are shown. Stage 0: Uncorrected/unpalliated ductal-dependent parallel pulmonary and systemic circulations. Maintenance of ductal patency is necessary for systemic perfusion, and prostaglandin E_1 is indicated. No human experimental data exist for measures such as hyperoxic or hypocapnic alveolar gas strategies that tend to reduce pulmonary vascular resistance, and such strategies should generally be avoided without significant monitoring of systemic oxygen delivery. The greatest improvement in systemic oxygenation occurs with the induction of hypercapnic ventilation. Stage 1: After surgical palliation of parallel circulation with relief of arch obstruction and limitation of pulmonary blood flow with a systemic-to-pulmonary artery shunt. Hypercapnia can improve cerebral more than systemic oxygen delivery. Stage 2: After superior cavopulmonary anastomosis. The cerebral and pulmonary circulations are in series, and hypercapnia can improve systemic arterial oxygen saturation and systemic oxygen delivery by increasing cerebral blood flow, superior vena cava flow, and therefore pulmonary blood flow. Stage 3: After superior and inferior cavopulmonary anastomoses (post-Fontan). No systematic data exist for alveolar gas manipulation. See references for details.

AVO_2D, arteriovenous oxygen saturation difference; CBF, cerebral blood flow; lactate, lactate or metabolic acid change; Q_p/Q_s, pulmonary/systemic blood flow ratio; rSO_2C, cerebral oxygen saturation by near-infrared spectroscopy; rSO_2S, somatic oxygen saturation by near-infrared spectroscopy; Sa_{O2}, arterial oxygen saturation; SvO_2, systemic venous saturation; TPG, transpulmonary pressure gradient; VO_2, oxygen consumption.

There are several large institutional and national registries of AAOCA patients, and the American Association for Thoracic Surgery (AATS) published evidence-based consensus management guidelines in 2017 [81]. Typically, referral occurs following an episode of exertional chest pain, with ischemic findings on electrocardiogram. Initial diagnosis is made by echocardiography, with characteristic color flow Doppler pattern, but ultimately cardiac CT with coronary angiography is confirmatory. Surgical intervention is offered to patients with certain risk profiles, namely those with a history of survived arrest, syncope in the setting of ventricular arrhythmia, anginal chest pain, or positive inducible ischemia with provocative stress testing. Asymptomatic patients with intra-arterial AAOLCA are always offered surgery due to the elevated risk of death with that variant. Asymptomatic patients with intra-arterial AAORCA who wish to participate in sports were historically referred for surgery, but current AHA/ACC guidelines now recommend they can safely participate with close follow-up after initial evaluation [82].

The surgical options depend on the type of lesion, and a full discussion is beyond the scope of this chapter, but includes coronary artery unroofing, pulmonary artery translocation, and direct coronary procedures such as reimplantation or osteoplasty [81]. Percutaneous coronary intervention and surgical bypass grafting play little to no role in the management of children and adolescents. Patients will require close lifetime surveillance, and even the following surgery remains at an increased risk of recurrent SCD [83]. If return to competitive athletics is considered, all patients with AAOCA should have an immediately available automated external defibrillator during these activities, as the most prevalent inciting event is malignant ventricular arrhythmia.

An anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare anomaly, affecting approximately 0.5% of children with CHD or around 1 in 300,000 live births. The embryology and clinicopathologic basis were first described in 1933 by Bland, White, and Garland, after whom the syndrome is sometimes named [84]. ALCAPA results from abnormal conotruncal septation, with anomalous development of the left coronary system, and can lead to chronic myocardial ischemia and early onset cardiomyopathy. Mortality is nearly 90% by age 1 year if left untreated, although there are rare case reports of individuals diagnosed in adulthood [85]. The mechanism of ischemia is multifactorial and dependent on which subtype is present. In the classic infant type, there is insufficient collateral coronary circulation, and severe early ischemia develops following the closure of the ductus arteriosus with a reduction in pulmonary vascular resistance and pulmonary artery pressure. These infants often present with failure to thrive from neonatal onset ischemic heart failure, or sudden death from lethal ventricular arrhythmias [86]. Much rarer is the adult type,

wherein an extensive intracoronary collateral circulation develops from a dominant right coronary artery system. These patients may remain clinically silent for decades, although with ongoing subclinical ischemia and fibrosis, eventually developing anginal symptoms, mitral regurgitation, and decompensated left ventricular heart failure [85], although diagnosis is sometimes made at autopsy [87]. The sentinel event in some adults is ventricular tachycardia (VT) or ventricular fibrillation (VF) with exertion, highlighting the ischemic mechanism in this lesion. Surgical management is indicated in all patients and involves coronary revascularization with the closure of the left main orifice and coronary bypass grafting, or the Takeuchi procedure [88]. Additionally, the placement of an internal defibrillator-cardioverters should be considered if provocative testing in the electrophysiology lab shows inducible ventricular dysrhythmias.

There are reports of successful resuscitation with ROSC in adult patients subsequently diagnosed with ALCAPA [89]. These authors comment on the unfavorable coronary anatomy in this disease as it relates to CPR. Specifically, aortic diastolic blood pressure is lowest during the recoil/non-compression phase of CPR and is much closer to right atrial and coronary sinus pressure, and left coronary perfusion is retrograde from the RCA into the PA via the left coronary system. This anatomy places a significant portion of the myocardium at risk for malperfusion during conventional CPR. Also, as the inciting event is often a shockable malignant ventricular arrhythmia, immediate application of a defibrillator is essential. This has even been reported in successful bystander CPR of individuals presenting with out-of-hospital cardiac arrest, subsequently found to have ALCAPA [90] (See Chapter 3 for further discussion of anomalous coronary artery lesions).

Mechanical circulatory support

MCS for those with advanced heart failure is increasingly used as either a bridge to a decision, heart transplantation, or destination therapy. The devices employed for such support differ by mechanism; thus, some are pulsatile in nature (e.g. Berlin Excor®), while some provide the continuous flow (e.g. Heartmate II® and Heartware®). The differences in flow determine aspects of the physical exam which are used to assess circulatory adequacy. Palpation of pulses commonly relied upon in the setting of native heart function may be untrustworthy or frankly absent in MCS patients who have a continuous flow device supporting the LV. Pulse oximetry may be inaccurate as well. Instead, the assessment of mean arterial pressure should be attempted using either non-invasive BP or automated BP devices. A mean arterial BP >50 mmHg is typically deemed acceptable to sustain organ perfusion. Evaluation of extremity perfusion may also yield important information on circulatory adequacy. It is noteworthy that mechanical device function is influenced by preload and afterload. So, for example, PAH may decrease preload to an LV assist device, as would hypovolemia or pulmonary embolism. Increased afterload, in the form of systemic hypertension, may worsen cardiac output. Conversely, hypotension from septic shock or routine sedation may not be tolerated as devices have little ability to augment their output in the setting of lower SVR.

The two most common causes of pre-arrest VAD failure are disconnection of the device from power or the driver, and failure of the driveline (the tube that passes through the skin to connect the pump to the external controller and power source). Therefore, in larger children on a continuous flow device, unresponsiveness or hypotension should prompt immediate assessment of all connections to power and examination of the power source itself. If connections are secure and batteries are charged, the use of an alternate controller should be considered. Thereafter, other causes of poor flow must be considered, such as RV dysfunction, cannula malposition, thrombosis, arrhythmia, etc. Inotropes can be used to treat RV dysfunction, just as anti-arrhythmics and even cardioversion can be employed. In the case of the Berlin Excor VAD, the most commonly used device in children, a palpable peripheral pulse is expected due to the pneumatically driven pulsatility of the machine. Examination of device membrane movement should be performed, and if lacking, driveline and power connections should be checked. A hand pump can be used to provide flow from the Berlin Excor VAD while airway management is undertaken. Other patient-related factors which may adversely affect circulation such as tension pneumothorax, pericardial tamponade, and PAH must also be considered [91].

Resuscitation of the continuous flow MCS patient who is deemed to have poor systemic perfusion after initial patient and VAD assessment should be managed according to standard resuscitation guidelines, to include chest compressions. Similarly, if the Berlin Excor patient does not have a palpable pulse with the use of the hand pump, chest compressions should be promptly started (see Table 25.6). Administration of medications and defibrillation should proceed according to conventional Pediatric Advanced Life Support recommendations [91].

The underlying disease states

In addition to specific concerns in the various anatomic categories of CHD, there is a wide spectrum of other diseases and syndromes with the propensity for CA. The unique pathophysiology of some of these diseases can influence both the efficacy of CPR and dictate unique considerations during an arrest. In this section, we will review some distinct resuscitation features in Williams-Beuren syndrome, anomalous coronary syndromes, arrhythmias, cardiomyopathies, and pulmonary hypertension.

Table 25.6 Resuscitation management by device type

Flow profile	Continuous	Pulsatile
Common devices	Heartmate II, Heartware	Berlin Excor
ECG for rhythm	Yes	Yes
Pulse present	Only if good native contractility	Yes
NIBP feasible	Only if good native contractility	Yes
CPR chest compressions/ meds	Yes	Yes
Defibrillation	Yes	Yes
Hand pump available	No	Yes

Source: Data from Pilarczyk et al. [141].

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Williams-Beuren syndrome

First described in 1961, Williams syndrome (WS) is a genetic disease caused by a microdeletion of region q11.23 on chromosome 7. Amongst the gene deletions typically present, it is the hemizygosity for the elastin gene that leads to the classic connective-tissue abnormalities and resultant arteriopathy that characterizes this syndrome. Most significantly, this manifests as supravalvular aortic stenosis (SVAS) as well as diffuse coronary stenosis, but biventricular outflow tract obstruction can also be present and adds to the risk profile. Importantly, while the typical phenotype is generally seen in older children, this disease may be occult in infants. Cases of recurrent unexplained cardiac arrests in young infants [92], rapidly progressive ischemic cardiomyopathy precipitating unprovoked CA [93], and sudden death during induction of anesthesia [94] have all been reported.

The mechanism of ischemia is multifactorial, but fundamentally, elastin loss creates inefficient hydrodynamics with widened pulse pressure, systolic hypertension, and diastolic hypotension. In addition, progressive intima-media hyperplasia leads to obstructive aortic lesions near the sinotubular junction, reduced diastolic coronary perfusion, and intrinsic coronary insufficiency from aneurysmal dilatation; all these factors place the myocardium at risk for ischemia, worsened by omnipresent left ventricular hypertrophy [95]. Tachycardia, inadequate preload, and reduction in systemic vascular resistance (SVR) will all accelerate this pathophysiology, and the rapid fall in cardiac output and diastolic coronary flow serves to perpetuate the ongoing ischemic process

Diagnosis is often pursued when unexplained ischemic electrocardiogram findings and hemodynamic instability manifest in a young child, with echocardiographic findings of high left ventricular outflow tract (LVOT) pressure gradient by spectral Doppler. Hemodyamic catheterization and angiography confirm the cardiac lesions, and genetic testing is diagnostic. Perioperative management of these children centers on maintaining adequate preload, avoiding tachycardia, and preventing sustained reduction in SVR. Despite caution and proper planning, CAs can occur and should be treated with pure vasopressor agents, rapid-acting beta-blockers such as esmolol if tachycardic, and judicious volume loading. Resuscitation can be refractory to standard measures; however, even requiring ECMO as a rescue maneuver until definitive diagnoses can be made, and corrective cardiac surgery is undertaken [94]. It should also be noted that delayed sudden death has been reported remote from procedural or anesthetic care, thought in retrospect to be secondary to malignant arrhythmia [96]. It is for this reason that many centers will admit children with confirmed WS even following routine procedures for overnight observation. See Chapters 8 and 27 for further discussion of Williams-Beuren Syndrome.

Arrhythmias

Appropriate management of ventricular arrhythmias with cardioversion, defibrillation, and pharmacotherapy is a vital component of standard Advanced Cardiac Life Support (ACLS) and Pediatric Advanced Life Support (PALS) algorithms. However, there are specific arrhythmogenic conditions that both predispose patients to cardiac arrest and yet may be exacerbated or perpetuated by standard therapies used during resuscitation.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disorder of cardiac calcium metabolism, caused by mutations in the RyR2 gene, among others[97]. It is a rare disorder with protean symptoms; universally present however is inducible rapid VT in children and young adults in response to catecholamines such as epinephrine. Presentation is generally unexpected syncope, convulsions, or sudden death, and the diagnosis is often elusive. Of note, this catecholamine trigger can be either *exogenous*, such as during vigorous exercise or stress, or *endogenous* as in the treatment of the ensuing arrest with epinephrine. The latter scenario can be vexing to caregivers, as the VT will be refractory to epinephrine boluses, and in fact, maintained and worsened by it. The diagnosis is suggested in previously well patients following a cardiac arrest after physical activity, whose ECG shows ventricular extrasystoles made more frequent with epinephrine, or characteristic bidirectional VT [98]. Even predominantly alpha-adrenergic vasopressor drugs such as norepinephrine used to treat post-arrest vasoplegia, can trigger a CPVT storm due to their beta-adrenergic effects [99]. Initial management should focus on the suppression of catecholamine drive with opioids and anesthetics. More directed treatment is beta blockers such as nadolol, antiarrhythmic therapy with flecainide, and ultimately placement of an ICD. Denervation procedures such as cardiac sympathectomy have also been employed with some success [100].

Another genetic disorder that can manifest malignant arrhythmias in response to stress or catecholamine trigger is the long QT syndrome (LQTS). There is a spectrum of different syndromes causing cardiac channelopathies, resulting in prolongation of the QT interval, with a predilection to the development of torsades-de-pointes and ventricular fibrillation. These congenital or hereditary variants of LQTS include Romano-Ward syndrome (RWS), Jervell and Lange-Nielson syndrome (JLNS), Timothy syndrome, Anderson-Tawil syndrome, among others, all of which have distinct associated genetic bases and clinical features [101]. There are also acquired types of LQTS, commonly drug-induced, but also related to profound electrolyte derangements, myocardial infarction, hypothyroidism; of note, these acquired risk factors also exacerbate the risk of cardiac events in patients with congenital LQTS. In some patients with CHD experiencing first episode syncope or arrest, the diagnosis of LQTS may be obfuscated by QTc-prolonging medications given in the perioperative setting as well as pre-existing right bundle branch block (RBBB), which can mask the prolonged QT interval [102]. Of particular concern for anesthesiologists caring for these patients are the numerous potential triggers that occur in the perioperative setting, many related to dynamic autonomic tone and reduced repolarization reserve. In addition to adequate analgesia, avoidance of hypothermia, and maintenance of cardioprotective electrolyte levels, attention must be paid to careful selection of anesthetic agents and other medications, as an exhaustive list has been implicated as triggers [103]. While propofol is generally thought to be safe, inhalational agents like sevoflurane can prolong the QTc, although they are commonly used without incident [104]. Finally, some consideration must be given to whether the

LQTS is drug-induced, in which case chemical pacing with isoproterenol may overdrive or suppress the VT, and congenital LQTS in which catecholamines will cause further sympathetic stimulation and exacerbate the ventricular arrhythmia. If any doubt exists, short-acting titratable beta blockade with esmolol may be a safer option [105]. See Chapter 22 for further discussion of arrhythmias and their treatment.

Cardiomyopathies and myocarditis

The cardiac anesthesiologist often is called to care for children with cardiomyopathies or presumed myocarditis and for imaging studies, cardiac catheterizations, and both cardiac and noncardiac surgery. These are often fragile patients, with limited cardiac reserve, and the potential for sudden cardiac arrest is omnipresent. Findings of increasing ectopy burden or declining systemic perfusion may signal acute decompensated heart failure with low cardiac output and a pre-arrest state. Patients with dilated cardiomyopathy (DCM) already suffer from poor systolic function with reduced left ventricular ejection and diminished myocardial perfusion, often making successful resuscitation from cardiac arrest unlikely. Attempts to reduce oxygen consumption, reduce LV afterload, and improve myocardial contractility with inotropes should be initiated early in the clinical course. In those with hypertrophic and restrictive phenotypes, inotropic support can be deleterious as it increases myocardial oxygen demand and often induces tachycardia, further reducing diastolic filling time. Inotropes can also be arrhythmogenic in both myocarditis and some cardiomyopathies [19]. Clinicians should recognize that the timely institution of ECMO, as a semi-elective procedure, may be lifesaving [11, 106]. As some types of cardiomyopathies and myocarditis may be reversible (i.e. if dysrhythmia-induced or infectious), ECMO can be considered as a bridge-to-recovery therapy in these contexts or as an interval step toward durable mechanical support for irreversible disease. Similarly, ablation of sympathetic tone and reduction in preload, as can occur with induction of anesthesia and initiation of mechanical ventilation, can precipitate arrest in these patients. Patients in this vulnerable category are often best served by the preemptive mobilization of ECMO resources and personnel prior to such maneuvers ("wet pump" on stand-by). As with many special scenarios, vigilance and prevention are preferable to salvage resuscitative efforts that may well be futile.

Pulmonary hypertension

Pulmonary hypertension (PH) is a significant cause of mortality in patients with CHD, specifically after cardiac surgery. In biventricular anatomy, it is defined as mean pulmonary artery pressure (mPAP) greater than 25 mmHg with indexed pulmonary vascular resistance (PVRI) of greater than 3 Wood units. In single ventricle patients, the definition can be modified to include a transpulmonary pressure gradient (TPG) of greater than 6 mmHg even with PAP below threshold values. PH from CHD can be broadly categorized into *pre-capillary* processes wherein increased pulmonary blood flow occurs from left-to-right shunt lesions (systemic to pulmonary shunts, ventricular septal defect, atrioventricular canal, etc.), or *post-capillary* elevations in PAP from left heart disease (intrinsic left ventricular dysfunction, severe left-sided AV valve stenosis, cor triatriatum, etc.). In addition to CHD, a wide array of other noncardiac processes can lead to the development of PH, including severe interstitial or alveolar lung disease, intrinsic pulmonary arterial vascular disease, thromboembolism, and others. Modern categorization systems such as those from the World Symposium on Pulmonary Hypertension [107] and, more applicable to pediatric disease, the Panama Classification from the Pulmonary Vascular Research Institute Pediatric Task Force [108], reflect this heterogeneity.

Chronic management of PH is beyond the scope of this chapter, but it is discussed elsewhere in this textbook and reviewed in recent guidelines from the AHA and American Thoracic Society [109]. In brief, therapeutics are broadly vasodilators and/or antiproliferatives, with vasodilators directed at either the endothelin, nitric oxide, or prostacyclin pathways. Many severely affected patients will be on combination therapy regimens with an endothelin receptor antagonist (Bosentan, Ambrisentan), a phosphodiesterase-5 inhibitor (Sildenafil, Tadalafil), and a synthetic prostacyclin analog (Epoprostenol, Treprostanil, Iloprost). It is critical to continue all maintenance medications throughout the perioperative period, as abrupt discontinuation, substitution, or dose reduction can be the precipitating factor in a deleterious and possibly fatal increase in PA pressure [110, 111].

The most feared sequelae of PH is the development of a PH crisis, which has a complex and dynamic pathophysiology. The highly muscularized and "reactive" pulmonary vascular bed in PH is vulnerable to many factors that can trigger this acute PVRI rise. Among them, pain, bronchospasm, acidosis, hypoxia, and hypercarbia [112] have been well-studied, and can commonly occur in the perioperative setting. As with many high-risk scenarios in congenital cardiac anesthesia, risk stratification and avoidance are preferable, highlighting the importance of careful planning. Once initiated, the process is rapidly progressive and can be quite challenging to rescue prior to cardiac arrest. These episodes are characterized by acute elevations in pulmonary vascular resistance index (PVRI) and pulmonary artery pressure (PAP), which ultimately precipitate right ventricular failure. The elevated RV afterload, coupled with decreased coronary perfusion from systemic hypotension, leads to myocardial ischemia. Subsequently, a multifactorial reduction in cardiac output occurs, as pulmonary blood flow and therefore LV preload fall, exacerbated by restricted filling from a shifting interventricular septum, and worsened by progressive ischemia. Abortive maneuvers to reverse this vicious cycle include inhaled pulmonary vasodilators, and systemic vasoconstrictors such as vasopressin to increase SVR and restore coronary perfusion.

There are unique features of a PH crisis that can render conventional CPR infective at restoring ROSC, specifically the challenge in generating sufficient pulmonary blood flow to fill the LV and produce systemic cardiac output. When cardiac arrest occurs in the context of a PH crisis outcomes are quite poor, with adult data suggesting a 6% survival [113]. Interestingly, however, a recent single-center study in pediatric in-hospital arrest found a 67% survival amongst those with

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Table 25.7 Cannulation strategies for ECPR[a]

Physiology	Peripheral cannulation		Central cannulation		Comments
	Venous	Arterial	Venous	Arterial	
Biventricular circulation	Internal jugular or femoral	Common carotid or femoral	Systemic venous atrium	Aorta	Left atrial decompression may be required.
Single ventricle or shunted physiology	Internal jugular	Common carotid	Systemic venous or common atrium	Aorta	Shunt restriction may be required; for carotid cannulation with an MBTS, cannula position can result in shunt overcirculation or occlusion.
Superior cavopulmonary anastomosis	Internal jugular and/or femoral	Common carotid	SVC and/or systemic venous or common atrium	Aorta	An additional venous cannula may be required
Fontan	Internal jugular and/or femoral	Common carotid or femoral	Fontan baffle	Aorta	An additional venous cannula may be required; pulmonary venous atrial drainage may be required

Source: Marino et al. [19]. Reproduced with permission from Wolters Kluwer Health, Inc.

ECPR, extracorporeal life support to support failed cardiopulmonary resuscitation; MBTS, modified Blalock-Taussig shunt; SVC, superior vena cava.

[a] General principles for efficient use of extracorporeal life support (ECLS) to support cardiopulmonary resuscitation include the following (i) Venoarterial ECLS should be used in all cases, (ii) Knowledge of venous anatomy and previously occluded vessels is critical for successful and timely deployment of ECLS, (iii) Central (transthoracic) cannulation may be considered in patients who have undergone a recent sternotomy, (iv) Peripheral (percutaneous) cannulation may be preferred for patients without recent sternotomy, and (v) ECLS cannulas should be large enough to provide complete cardiac output (cardiac index >2.5 L/min/m^2). If extracorporeal membrane oxygenation flow is limited by inadequate venous drainage, secondary drainage sites should be considered.

echocardiographic evidence of PH, similar to the rate in children without PH in the study. Notably, there was a more than twofold higher use of inhaled nitric oxide in the PH cohort, highlighting the crucial importance of specific therapies directed at the underlying cause of the arrest [114]. Ventilation should be carefully managed; while acute hyperventilation may reduce unfavorable hypercarbia and acidosis, it may also increase mean airway pressures and end-expiratory lung volumes, reducing RV filling through harmful cardiopulmonary interactions. In addition to standard resuscitative drugs, pulmonary vasodilator therapy, by either inhalational or intravenous routes, may be beneficial during the arrest. Ultimately, timely cannulation onto ECLS as a bridge to recovery or transplant should be considered if CPR is ineffective at restoring circulation. In this group of patients, once stabilized the creation of a restrictive atrial communication via septostomy in the catheterization lab can allow a right-to-left shunt to preserve cardiac output and systemic oxygen delivery, even in the absence of pulmonary blood flow. This may allow separation from ECMO, albeit with often marked hypoxemia; under investigation currently are devices that allow individualized flow regulation through the atrial shunt [115]. See Chapter 33 for further discussion of PH.

Open-sternum CPR

In the operative cardiac surgery patient, the postoperative patient with the open sternum, or the E-CPR patient who will undergo central ECMO cannulation, open cardiac massage is necessary to maintain as much cardiac output as possible while the surgeon cannulates the aorta and right atrium. Where possible the surgical assistant should perform an open cardiac massage while the primary surgeon prepares to cannulate. An arterial catheter is usually present and should guide the force of open cardiac massage. Additional resuscitative measures, that is, drugs and defibrillation, should be pursued while preparations for cannulation are occurring. Distraction from the resuscitation, with ineffective cardiac compressions because of cannulation preparation, or one surgeon attempting to perform both open cardiac massage and cannulate, should not occur. An organized, role-based approach to CPR will reduce the period of no-flow/low-flow until ECMO or emergent CPB is established. This complex situation is particularly amenable to team simulation training. (See below). Cannulation strategies for ECPR according to physiology and stage of palliation are displayed in Table 25.7 and mechanical device support strategies are displayed in Figure 25.4. See Chapter 37 for further discussion of ECMO in CHD.

Adjunctive CPR techniques for the CHD patient

Interposed abdominal compression CPR

As mentioned above, chest compressions during conventional CPR may impede venous return to either the right heart or pulmonary arteries, and in the setting of cavopulmonary anastomoses, may limit cerebral blood flow. In addition, low diastolic BP during CPR, whether exacerbated by aortopulmonary shunts or pre-arrest hypotension, may compromise coronary perfusion pressure. One CPR adjunct that may influence both of these conditions is IAC-CPR.

IAC-CPR is a technique in which force is applied to the abdomen during the recoil phase of chest compressions. It

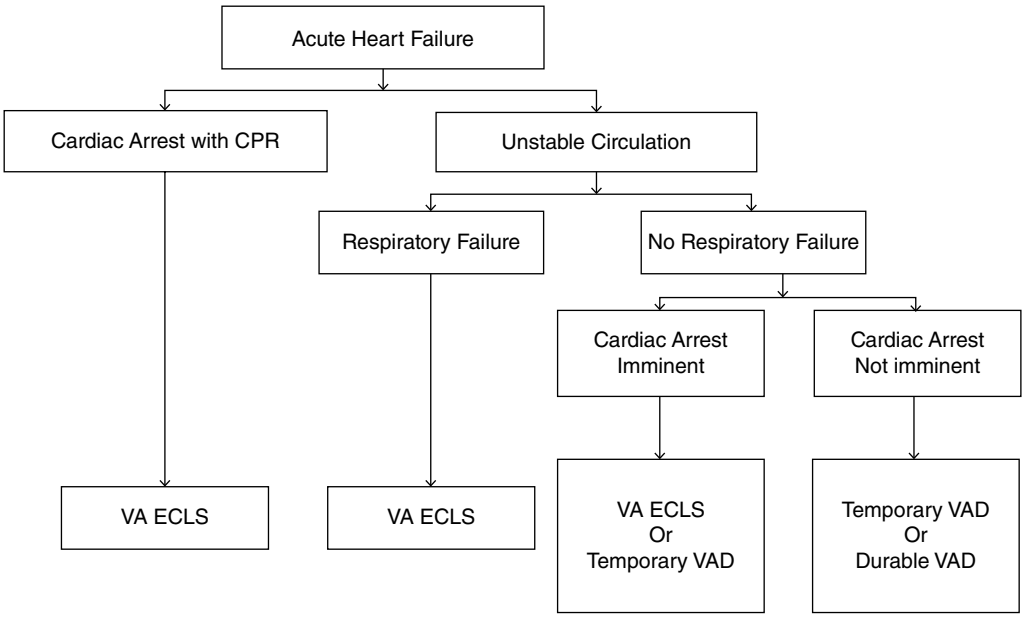


Figure 25.4 Mechanical circulatory support device strategy in rapidly deteriorating children with heart disease.[4,8,35,81,144,271–276,283,298,302,303,312,325–327,331,386,650,659] Choice of ventricular assist device (VAD) depends on patient size and need for left ventricular or biventricular support. Examples of temporary VADs include centrifugal pump extracorporeal life support (ECLS) without oxygenator, Impella, and Tandem Heart. Examples of durable VADs include Berlin Heart EXCOR, Thoratec paracorporeal VAD, HeartMate, HeartWare, and total artificial heart/SynCardia. CPR indicates cardiopulmonary resuscitation; and VA ECLS, venoarterial ECLS.

includes all elements of conventional CPR, thereby serving as an adjunct to traditional resuscitation. IAC-CPR works by external force transmission through the abdomen to the aorta. This leads to an increase in aortic diastolic pressure and enhanced retrograde flow to the coronary arteries and prograde flow to the brain. Hemodynamic effects are similar to intra-aortic balloon counterpulsation or external counterpulsation [116]. IAC-CPR also results in hydrostatic compression of intra-abdominal veins, which advance blood into the thoracic compartment during the relaxation phase of chest compressions. This refilling of the intrathoracic blood pool improves cardiac output with subsequent chest compressions. Finally, IAC-CPR augmentation of baseline venous pressure coupled with maintenance of an adequate arteriovenous gradient overcomes capillary closing pressure and thereby improves vital organ perfusion [117].

IAC-CPR has been evaluated in both animals and human adults. In a swine ventricular fibrillation model, animals receiving IAC-CPR as opposed to conventional CPR during arrest demonstrated greater systolic and diastolic BP, coronary perfusion pressure, and end-tidal CO_2 (as a surrogate measure of cardiac output). Return of spontaneous circulation (ROSC) was greater in the IAC-CPR cohort, and neurologic examinations in survivors who received IAC-CPR were superior to those who underwent conventional CPR [118].

Human studies on IAC-CPR have yielded similar benefits. Data from four randomized clinical trials of IAC-CPR have shown improved resuscitation rates and survival for patients experiencing IHCA [119]. Formal meta-analysis of randomized clinical trials of IAC-CPR versus conventional CPR revealed improvement in the rate of ROSC by 10.7% ($p = 0.006$) and a trend toward increased hospital discharge with the intact neurologic function of 8.7% ($p = 0.06$). When meta-analysis was limited to in-hospital trials ($n = 279$), ROSC was 52% with IAC-CPR versus 26% with conventional CPR ($p < 0.0001$). This suggests that only four patients would need to be treated with IAC-CPR to achieve ROSC in one additional patient. IAC-CPR has been recommended as an acceptable alternative to conventional CPR for in-hospital resuscitation (Class IIb recommendation per AHA guidelines) [120]. However, as yet, no published pediatric data upon which to base recommendations exist. Resuscitation registry information comparing judicious use of IAC-CPR and conventional CPR within the same patient at the discretion of the resuscitation team (including arterial waveforms, other monitor data, and outcomes) is being gathered.

In theory, IAC-CPR could be beneficial in CHD patients who are dependent upon passive flow to the lungs, those who experience limitation of PBF through pulmonary obstruction or PAH, and those with elevated ventricular filling pressures. The technique's ability to raise diastolic BP could augment cerebral blood flow and coronary perfusion pressure. This effect upon diastolic BP is thought to be critical to the achievement of ROSC in both adults and children. Paradis et al. found that adults who do not generate >16 mmHg diastolic BP during resuscitation do not experience ROSC [121]. Similarly, Berg et al. showed that the attainment of a threshold diastolic BP of 25 mmHg in children <1 year and 30 mmHg in those >1 year raised the probability of ROSC [72]. Preliminary mathematical modeling of single ventricle anatomy (personal communication) suggests that IAC-CPR raises overall cardiac output during CPR, including cerebral blood flow, and does not augment PBF in single-ventricle patients at the expense of systemic perfusion. That IAC-CPR could compromise cerebral blood flow through increased venous pressures seems unlikely given the

aforementioned animal findings, and the recently determined correlation of diastolic BP with cerebral blood flow during CPR microsphere experiments in pigs [122].

Head-up CPR

CPR is typically performed with the patient in the supine position. However, some information in animal models of arrest has demonstrated that elevation of the head during CPR may have a beneficial effect upon intracranial pressure, cerebral perfusion pressure, and brain blood flow [123]. With the head up (usually around 30°) gravity helps to drain venous blood from the brain back to the heart, leading to greater intracardiac filling between chest compressions and lower intracranial pressure. This, in turn, lowers impedance to forward cerebral blood flow with subsequent chest compressions. These benefits have only been seen when using an impedance threshold device and/or active compression-decompression device [see below] to generate more negative intra-thoracic pressure and greater cardiac output, and they have not been uniformly validated [124]. Clinical studies, especially in pediatrics, have yet to be conducted.

Intrathoracic pressure regulation: active compression decompression CPR and the impedance threshold device

The ability to use the thorax as a compartment that fills and empties into the systemic circulation is referred to as the thoracic pump mechanism of CPR. This mechanism can be augmented to increase cardiac output through the manipulation of intrathoracic pressures. Reduction of intrathoracic pressure during CPR diastole encourages inflow to the thoracic cavity, and chest compressions which raise intrathoracic pressure to expel blood to arterial vessels. Active compression-decompression CPR (ACD-CPR) uses a suction device to repetitively pull up and push down on the chest. The upward suction enhances chest recoil, creating greater negative intrathoracic pressure. This results in augmentation of venous return to the heart and lungs and preload to the LV; it also lowers intracranial pressure and increases coronary and cerebral perfusion pressure. ACD CPR can be combined with the use of an impedance threshold device (ITD). The ITD works by transiently impeding airflow into the lungs during chest wall recoil (but not during positive pressure ventilation). This also creates negative intrathoracic pressure which pulls more venous return to the heart to augment cardiac output. Both these devices have been tested in animals and humans, with the combination demonstrating a survival benefit relative to conventional CPR, prompting Food and Drug Administration (FDA) approval [125]. Though studies of young animals have been conducted with ACD-CPR plus the ITD, clinical investigation in children has not been accomplished to date.

CPR coaching

Emphasis on the performance of high-quality CPR has prompted a recent investigation into the advisability of having a trained CPR coach present during resuscitation. Cheng et al. randomized CPR teams from four United States and Canadian centers to have a trained CPR coach vs. no CPR coach. CPR coaches were made responsible for providing real-time verbal feedback regarding CPR performance to compressors, and caregivers had access to real-time CPR quality data from the defibrillator. CPR coaching resulted in absolute improvements in mean chest compression depth compliance, mean chest compression fraction, and mean pre-, post-, and perishock pause duration [126]. Kessler et al. then reviewed videotape from the simulated pediatric arrests in the Cheng study and performed a secondary analysis. CPR-coached teams demonstrated improved verbalization before pauses, decreased pause duration, shorter pauses with intubation, and better task coordination than their counterparts [127]. Shorter pause duration is associated with higher rates of ROSC and survival to discharge [128], and current guidelines recommend limiting interruptions in chest compressions to <10 seconds due to adverse effects upon coronary perfusion pressure [59]. Though the studies to date on this subject have all utilized simulated scenarios, the notion that a coaching intervention can significantly improve team choreography, and perhaps CPR quality, is important. The effect upon real outcomes awaits investigation.

KEY POINTS: ADJUNCTIVE CPR TECHNIQUES IN CHD

- CPR avoidance via astute pre-arrest management represents the best strategy for the care of infants and children with CHD.
- Once an arrest has occurred, the tenets of high-quality conventional CPR apply directly to the population with CHD, even as some heart defects and conditions may limit CPR effectiveness.
- E-CPR should be considered early in the course of resuscitation that has failed to achieve ROSC to obtain optimal outcomes.
- Adjunctive CPR techniques, such as IAC-CPR and CPR coaching, have theoretical benefits but require clinical validation in the pediatric cardiac population.

Simulation/education

The education of patient caregivers is a key determinant of survival after CA. The current evidence supports that adherence to the guidelines during CPR improves patient survival. Unfortunately, in both simulated and real CAs, providers often fail to deliver the right depth, rate, and recoil of chest compressions [129, 130]. The current certification training programs from the AHA provide varying rates of skill acquisition. Poor skill performance of providers is seen even after 3 months of learning activity. Increasing the frequency of training may improve the efficacy of training, protect against skill deterioration, enhance performance during patient care, and improve patient outcomes.

In addressing this issue, the AHA's Resuscitation Quality Improvement (RQI) program utilizes a spaced training design, where CPR skills are practiced at least every 3 months. In contrast with high-dose, low-frequency training,

low-dose, high-frequency booster training is effective in improving retention[131]. Studies have shown that short-duration just-in-time CPR training is more effective when performed monthly than quarterly [132, 133]. In pediatric residents, a short deliberate practice-based training session was found effective in achieving mastery learning, and it was maintained in 90% of learners two months after training [134]. Training the learners in a variant of deliberate practice, called rapid cycle deliberate practice, has been associated with improved performance and shorter training times, along with a decrease in decay compared to a standard simulation approach [135–137].

Team training

Team training has been a component of AHA's resuscitation education since 2005. It is directed toward optimizing teamwork, communication, leadership, and other aspects of crisis resource management. IHCA is usually treated by a team of health care professionals. Code teams exposed to composite resuscitation team training are more likely to adhere to resuscitation guidelines [138]. The introduction of a CPR coach, a team member whose primary responsibility is to provide real-time coaching and feedback on chest compression (CC) performance during cardiac arrest can improve the quality of CC during a simulated cardiopulmonary arrest when a CPR feedback device is in use [126].

With advances in technology and web-based connectivity, there is an increasing focus on the use of new platforms and strategies for healthcare provider education. New gaming environments are available, which facilitate CPR skill training, retention, teamwork, and situational awareness [139, 140]. Screen-based education delivery provides the advantage of consistency, the lack of a need for an instructor, lower cost, and flexibility with time and space for learning. With the increasing presence of medical professionals in social media, the incorporation of social media into educational frameworks provides opportunities for increased connectivity, engagement of learners in knowledge creation and dissemination, and reaching learners with varying learning styles through different modalities.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

16 Topjian AA, Raymond TT, Atkins D, et al. Part 4: pediatric basic and advanced life support: 2020 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142(16_suppl_2):S469–523. This reference contains the 2020 American Heart Association guidelines for cardiopulmonary resuscitation for pediatric basic and advanced life support, excluding the newborn period. These guidelines and recommendations are based on the current best available resuscitation science. These guidelines are intended to be a resource for lay rescuers and health care providers to identify and treat infants and children in the pre-arrest, intra-arrest, and post-arrest states.

19 Marino BS, Tabbutt S, Mac Laren G, et al. Cardiopulmonary resuscitation in infants and children with cardiac disease: a scientific statement from the american heart association. Circulation 2018;137(22): e691–782. This is a scientific statement from American Heart Association, written by an appointed group who reviewed the literature from 1966 to 2015, addressing resuscitation in children with heart disease. This statement is meant for caregivers of children with heart disease in the pre-hospital and in-hospital settings.

23 Morgan RW, Kirschen MP, Kilbaugh TJ, et al. Pediatric in-hospital cardiac arrest and cardiopulmonary resuscitation in the united states: a review. JAMA Pediatr 2021;175(3):293–302. This is a narrative review summarizing the current knowledge and recommendations regarding pediatric in-hospital cardiac arrest (IHCA) and cardiopulmonary resuscitation. Pediatric IHCA occurs frequently and has a high mortality rate. Early identification of risk, prevention, delivery of high-quality CPR, and post cardiac arrest care can maximize the chances of achieving favorable outcomes.

28 Topjian AA, de Caen A, Wainwright MS, et al. Pediatric post-cardiac arrest care: a scientific statement from the american heart association. Circulation 2019;140(6):e194–233. This is a scientific statement from American Heart Association on post-cardiac arrest care and is a result of consensus process that included specialists across multiple disciplines who analyzed the past 20 years of pediatric cardiac arrest, adult cardiac arrest, and pediatric critical illness peer-reviewed published literature. This statement summarizes the epidemiology, pathophysiology, management, and prognostication after return of sustained circulation after cardiac arrest and it provides consensus on the current evidence supporting elements of pediatric post-arrest care.

37 Cheng HH, Rajagopal SK, Sansevere AJ, et al. Post-arrest therapeutic hypothermia in pediatric patients with congenital heart disease. Resuscitation 2018;126: 83–9. This study compared the safety/efficacy outcomes in post-arrest congenital heart disease (CHD) patients treated with therapeutic hypothermia (TH) versus controls not treated with TH. The data from this study has shown that pediatric CHD patients who suffered cardiac arrest can be treated effectively and safely with TH, which may decrease the incidence of seizures.

47 Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84. This is a clinical practice guideline for acute kidney injury (AKI), from the group – Kidney Disease Improving Global Outcomes (KDIGO). This guideline focused on four key domains (1) AKI definition, (2) prevention and treatment of AKI, (3) contrast induced AKI and (4) dialysis interventions for the treatment of AKI.

81 Brothers JA, Frommelt MA, Jaquiss RDB, et al. Expert consensus guidelines: anomalous aortic origin of a coronary artery. J Thorac Cardiovasc Surg 2017;153(6):1440–57. Anomalous aortic origin of a coronary artery is associated with sudden cardiac death. This reference provides the 2016 American Association for Thoracic Surgery evidence-based guidelines for the management of anomalous aortic origin of a coronary artery.

91 Peberdy MA, Gluck JA, Ornato JP, et al. Cardiopulmonary resuscitation in adults and children with mechanical circulatory support: a scientific statement from the American Heart Association. Circulation 2017;135(24):e1115–34. This is a scientific statement from the American Heart Association which highlights the recognition and treatment of cardiovascular collapse or cardiopulmonary arrest in an adult or pediatric patient who has a ventricular assist device or total artificial heart. Expert consensus recommendations are provided for the role of external chest compressions in such patients.

109 Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132(21):2037–99. Pulmonary hypertension is associated with diverse cardiac, pulmonary, and systemic diseases in neonates, infants, and older children and contributes to significant morbidity and mortality. In a joint effort from the American Heart Association and American Thoracic Society, a panel of experienced clinicians and clinician-scientists was assembled to review the current literature and to make recom-

mendations on the diagnosis, evaluation, and treatment of pediatric pulmonary hypertension. This publication presents the results of extensive literature reviews, discussions, and formal scoring of recommendations for the care of children with pulmonary hypertension.

126 Cheng A, Duff JP, Kessler D, et al. Optimizing CPR performance with CPR coaching for pediatric cardiac arrest: a randomized simulation-based clinical trial. Resuscitation 2018;132 : 33–40. This is a multicenter, prospective randomized trial evaluating if integrating a trained CPR coach in resuscitation team can improve CPR quality during simulated pediatric cardiopulmonary arrest (CPA). This study demonstrated enhanced CPR quality metrics after integration of a trained CPR coach into resuscitation team while in the presence of CPR feedback technology.

CHAPTER 26
Anesthesia for Left-to-Right Shunt Lesions

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Introduction

Left-to-right shunt lesions are the most common congenital heart defects, accounting for approximately 50% of all lesions. They are defined by a communication between the systemic and pulmonary circulations that allows shunting of well-oxygenated (systemic) blood to the less-oxygenated (pulmonary) circuit. This definition applies whether the associated structures are located on the left or right side anatomically. For instance, a child with a ventricular septal defect (VSD) and L-transposition of the great arteries (ventricular inversion) will shunt blood from the right-sided systemic ventricle to the subpulmonic, lower pressure left-sided ventricle. The degree of shunting through a left-to-right shunt lesion may be limited by the size of the defect or the resistance to blood flow on either side. For example, shunting between high-pressure systems like the ventricles through a large VSD is dependent on the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR). In contrast, left-to-right shunting through a large atrial septal defect (ASD) occurs primarily during atrial contraction and is dependent on the relative diastolic compliances of both right and left ventricles into which the atria eject. Hemoglobin concentration is another contributing factor to the amount of left-to-right shunting. Elevated blood viscosity, which rises with increasing hemoglobin concentration, increases both PVR and SVR. The net effect is a reduction in left-to-right shunting. The physiologic decline in hemoglobin concentration in the first 3 months of life is thought to have a substantial role in the normal fall of PVR after birth and may contribute to the exacerbation of symptoms related to left-to-right shunting.

All left-to-right shunts produce a volume burden on the cardiovascular system, the effects of which vary according to the location of the shunt. Chamber dilation and hypertrophy, be it left, right, atrial, or ventricular, occur in structures that are involved in the pathway of the shunted volume (Figure 26.1). Shunting at the atrial level, such as through an ASD, results in an increased volume load in both atria and the right ventricle. Shunting through a VSD results in an increased volume load in both ventricles and the left atrium.

Shunting at the level of the great arteries results in an increased pulmonary artery blood flow, which increases pulmonary venous return to the left atrium. The extra shunt

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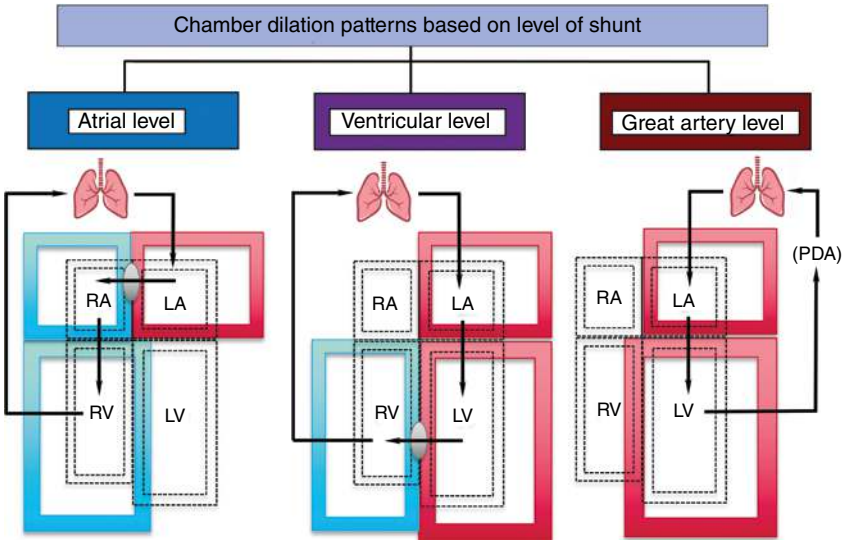


Figure 26.1 Schematic diagram of heart chamber dilation patterns based on level of the shunt. Black arrows represent the flow pathway of left-to-right shunted blood. Dashed lines represent normal chamber size. Red or blue boxes represent chamber dilation. Abbreviations: LA, left atrium; LV, left ventricle; PDA, patent ductus arteriosus. RA, right atrium; RV, right ventricle.

volume dilates the left atrium and leads to increased left ventricular end-diastolic volume and left ventricular stroke work by the Frank-Starling mechanism. The left ventricle also gradually dilates and hypertrophies, producing increased left ventricular end-diastolic pressure followed by increased left atrial pressure. Shunting at the level of the great arteries also produces a decrease in diastolic blood pressure from runoff of blood into the low-pressure pulmonary circuit after the closure of the aortic valve. Low diastolic pressures decrease coronary perfusion, potentially creating ischemia from decreased myocardial oxygen delivery in the setting of increased oxygen demand from the hypertrophied ventricle. The final result is pulmonary edema from pulmonary venous congestion and left heart failure. While the right atrium and ventricle are spared the volume loading is seen in the left-sided chambers, as PVR increases over time, there is an increased pressure burden on the right ventricle and eventual right heart failure.

Prolonged exposure of the pulmonary vasculature to increased flow and pressure results in a fixed increase in PVR. When PVR exceeds the SVR, the direction of the shunt can reverse and result in chronic cyanosis and erythrocytosis. Shunt reversal is more likely and occurs sooner with large defects distal to the tricuspid valve, but can be seen with any form of long-standing left-to-right shunt. When the elevated PVR causing right-to-left shunting becomes irreversible, this is known as Eisenmenger syndrome.

Figure 26.2 presents a schematic summary representation of the pathophysiology of the left-to-right shunting lesions and the factors that influence the degree of shunting at each level. Note that the four principal outcomes of RV failure, pulmonary edema, LV failure, and Eisenmenger physiology are possible with a long-standing shunt at any level. For example, although shunting at the atrial level does not create a direct volume burden on the left ventricle, if it eventually produces pulmonary hypertension to a degree that right ventricle (RV) pressure exceeds left ventricle (LV) pressure, the ventricular septum will shift leftward and impair LV function.

The normal compensatory mechanisms that maintain systemic cardiac output and myocardial performance in the patient with a left-to-right shunt include the Frank-Starling mechanism, the sympathetic nervous system, and hypertrophy of the myocardium. Manifestations of these compensatory mechanisms include sweating and tachycardia. Infants are also often tachypneic because of decreased lung compliance associated with increased pulmonary blood flow. Tachypnea impairs feeding, and growth failure develops from both decreased caloric intake and increased caloric utilization. Although significant left-to-right shunts can induce heart failure, infants rarely manifest peripheral edema or jugular venous distension like adults. The most consistent sign of right-sided failure in an infant is hepatomegaly.

Anesthetic management for left-to-right shunt lesions should be individualized to the patient, but certain generalities do exist. Premedication with intravenous or oral drugs such as midazolam (0.05–0.1 mg/kg IV or 0.75–1.0 mg/kg PO) can be safely administered for the purpose of decreasing anxiety and providing more controlled induction of anesthesia [1]. Standard American Society of Anesthesiologists (ASA) monitors, along with the use of invasive arterial and central venous pressure monitoring and careful attention to urine output are recommended for all cases involving cardiopulmonary bypass (CBP). Transesophageal echocardiography (TEE), cerebral oximetry, and cerebral blood flow monitoring are also useful monitoring adjuncts (see Chapters 14 and 15 for a more detailed discussion). Rarely, patients will present with severe, poorly controlled congestive heart failure (CHF) and be intolerant to the myocardial depressant effects of inhalational anesthetics. For this group of patients, intravenous (IV) anesthesia is preferred, with common agents including fentanyl, midazolam, and dexmedetomidine [2–5]. In most situations, however, inhalation induction with sevoflurane is a viable option when IV access is not initially available.

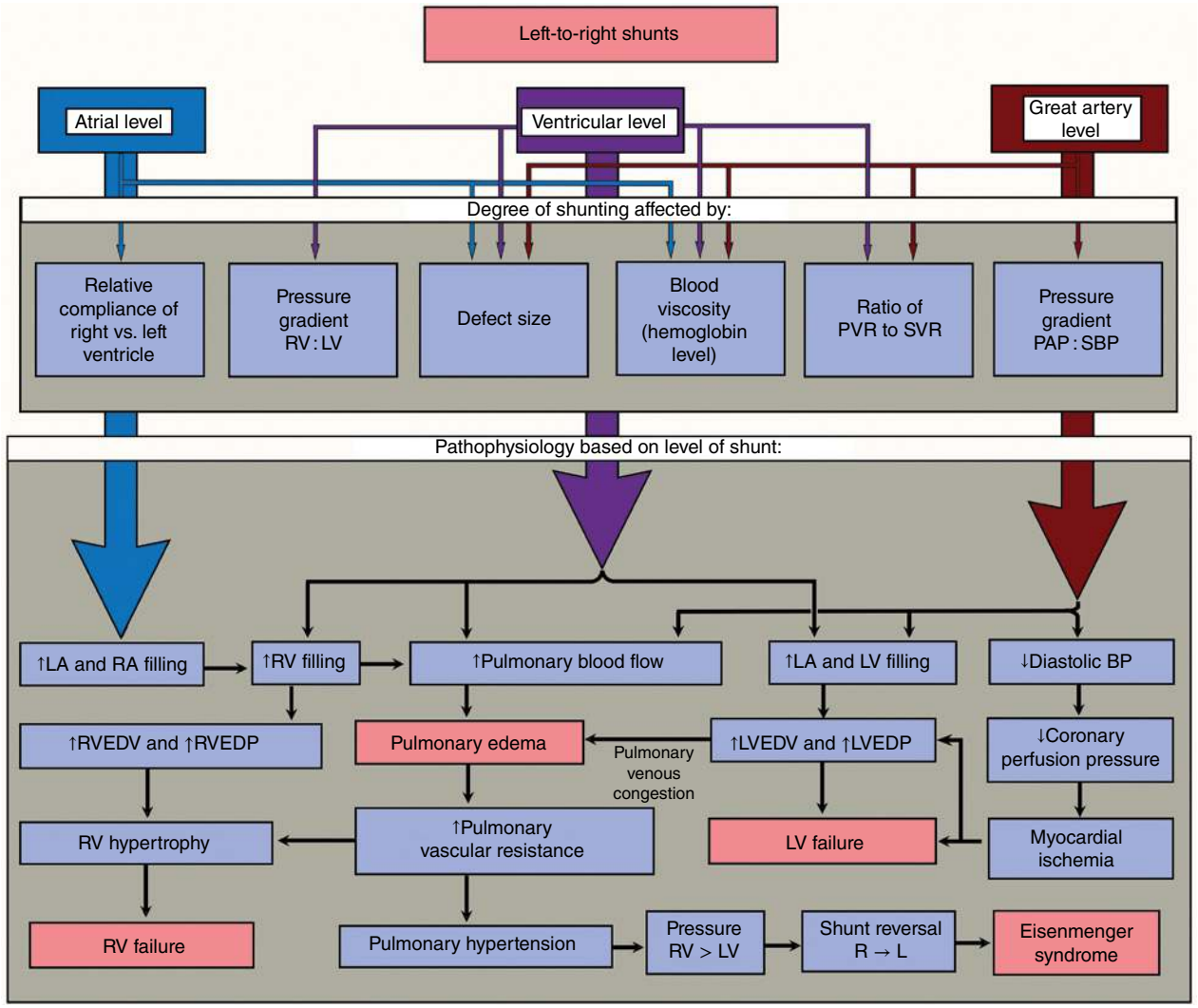


Figure 26.2 Pathophysiology of left-to-right shunting lesions. The flow diagram depicts factors that affect left-to-right shunting at the atrial, ventricular, and great artery levels and the pathophysiology produced by these shunts. A large shunt at any level can result in RV failure, LV failure, and pulmonary edema. Increased pulmonary blood flow leads to pulmonary hypertension and eventually Eisenmenger syndrome, characterized by irreversible right-to-left shunting. Abbreviations: BP, blood pressure; LA, left atrium; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; R, right; L, left. See text for detailed discussion. RA, right atrium; RV, right ventricle; LV, left ventricle; RVEDP, right ventricular end-diastolic pressure; RVEDV, right ventricular end-diastolic volume; SBP, systemic blood pressure; SVR, systemic vascular resistance.

Additional anesthetic issues include avoidance of air bubbles in IV lines to prevent paradoxical emboli. The anesthesiologist must also be cognizant of the pulmonary vasodilatory effect of oxygen and hypocarbia and manipulate ventilation in order to balance the PVR and SVR. Such measures generally include minimizing the fraction of inspired oxygen (FiO_2) and avoiding hyperventilation (maintaining the pressure of carbon dioxide ($PaCO_2$) between 40 and 50 mmHg).

Patent ductus arteriosus

Incidence, anatomy, and natural history

Isolated persistent patent ductus arteriosus (PDA) occurs in approximately 1 in 2,500 to 1 in 5,000 live births. The incidence is higher for premature births and PDA is two to three times more common in females than in males [6]. PDA is also found as part of other complex CHDs and is usually the source for pulmonary or systemic blood flow in patients with a functional single ventricle before palliative repair.

The ductus arteriosus is a vascular communication between the descending aorta and pulmonary artery. Embryologically, it arises from the distal portion of one of the sixth paired aortic arches [7]. It most commonly originates from the aorta, just distal to the left subclavian artery, and attaches to the left pulmonary artery (Figure 26.3) [8].

The ductus arteriosus is an essential component in normal fetal circulation; it becomes functionally closed within 10–15 hours after birth and permanently closes by thrombosis, intimal proliferation, and fibrosis in the first 2–3 weeks. Functional closure is initiated by several mechanisms

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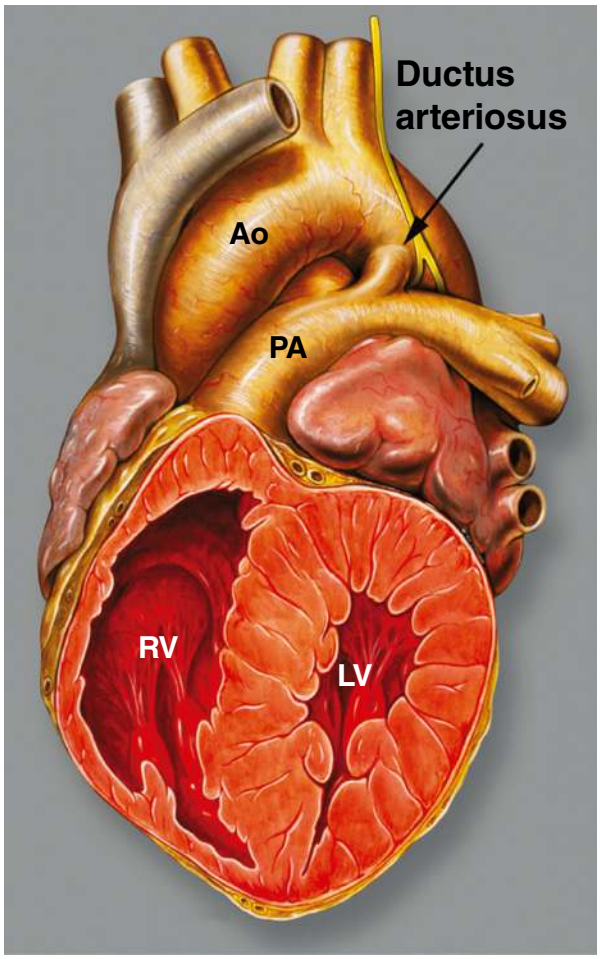


Figure 26.3 Patent ductus arteriosus. Ao, aorta; LV, left ventricle; P, pulmonary artery; RV, right ventricle. The yellow structure is the recurrent laryngeal nerve. (Source: Patrick J. Lynch, Medical Illustrator; C. Carl Jaffe, MD, Cardiologist / Wikimedia Commons / CC BY 2.5. https://en.wikipedia.org/wiki/File:Heart_patent_ductus_arteriosus.jpg.)

including aeration of the lungs, removal of prostaglandins produced in the placenta, increased arterial PO_2, and release of vasoactive substances (bradykinins, thromboxanes, and endogenous catecholamines) [6, 7, 9, 10].

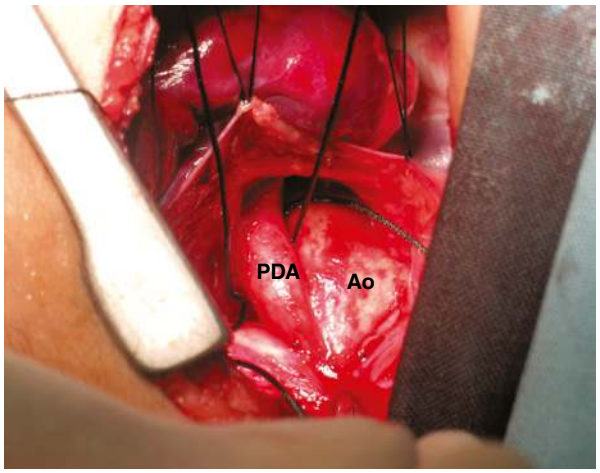
The consequences of a PDA left untreated depend on many factors. A small PDA may be hemodynamically insignificant and unrecognized. The larger the PDA and left-to-right shunt, the more likely the progression to CHF, pulmonary hypertension, and if chronic and/or extreme, reversal of the shunt. In premature infants, PDA may result in increased morbidity from associated respiratory distress syndrome, necrotizing enterocolitis, and intracranial hemorrhage.

Pathophysiology

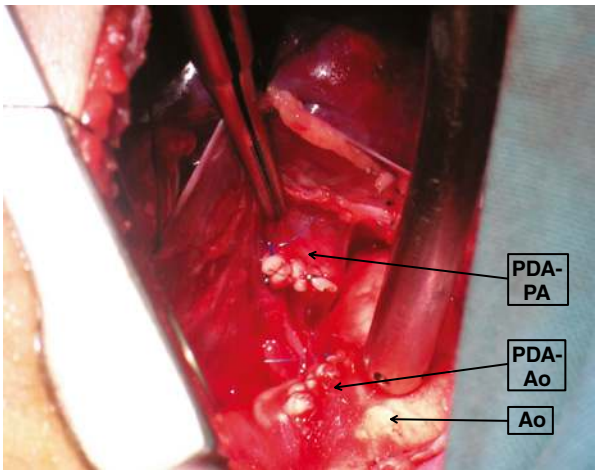
As a PDA represents a shunt at the level of the great vessels, the degree of left-to-right shunting depends on the dimensions of the PDA, the ratio of PVR and SVR, the ratio of PA pressure to systemic blood pressure, and blood viscosity as determined by the hemoglobin level. Ductal dimensions of importance include diameter and length. Larger diameters and shorter lengths produce less resistance, with the potential to allow greater flow. In patients with large PDAs, the diastolic runoff into the pulmonary artery results in lowered aortic diastolic pressure, which may increase the risk of myocardial ischemia, especially in the presence of anemia or lowered SVR.

Surgical and transcatheter approaches and outcomes

In premature newborns, the initial management of PDA is typically pharmacological closure using cyclo-oxygenase inhibitors such as ibuprofen, indomethacin, or acetaminophen [11, 12]. Cyclo-oxygenase inhibitors reduce the synthesis of prostaglandins, which would otherwise act to keep the PDA. Surgical treatment is usually reserved for patients who fail medical therapy. Surgical options include posterolateral thoracotomy with ligation or division of the PDA [13] (Figure 26.4), video-assisted thoracoscopic surgery (VATS), and robotically assisted total endoscopic closure [14]. These



(A)



(B)

Figure 26.4 Surgical ligation of a patent ductus arteriosus (PDA) via thoracotomy. (A) The PDA has been dissected and secured with ligatures, (B) Divided and oversewn PDA. Abbreviations: Ao, aorta; PDA-Ao, aortic end of PDA; PDA-PA, pulmonary artery end of PDA. (Source: Reproduced with permission from CTSNet.org.)

approaches have mortality approaching 0% and minimum morbidity; however, mortality rates in premature neonates are slightly higher. Complications of surgical treatment include bleeding, chylothorax, vocal cord paralysis (injury to the recurrent laryngeal nerve), pneumothorax, atelectasis, recurrence of patency, and inadvertent ligation of the pulmonary artery or descending aorta. Advantages of VATS compared to thoracotomy include decreased pain, decreased hospital cost (secondary to decreased hospital stay), and avoidance of post-thoracotomy syndrome (rib fusion, chest wall deformities, scoliosis, and compromise of pulmonary function). Disadvantages of VATS include intraoperative oxygen desaturation and hypercarbia, as well as higher morbidity during the surgical learning curve [15–17]. The use of robotic assistance achieves similar outcomes but with longer surgical times because of increased complexity [14, 18].

While surgical techniques are still employed, PDA closure is now most commonly accomplished in the cardiac catheterization laboratory. Techniques include the use of a variety of devices, including coils, vascular plugs, and umbrella-type occluders. Risks of transcatheter approaches include arrhythmias, embolization of the device, and incomplete closure [19–23]. However, these methods are considered safe, efficacious, and cost-effective when compared to surgical closure [24, 25]. Historically, there have been size limitations for use in small infants, but newer devices may allow for transcatheter closure in patients less than 1 kg with favorable anatomy [18–23]. See Chapters 19 and 34 for further discussion of transcatheter PDA occlusion.

Anesthetic considerations

The anesthetic management for PDA ligation depends on factors such as the patient's clinical condition, prematurity, coexisting disease, body weight, and surgical technique. Large volume venous access (which may be a 22- or 24-gauge IV in a premature infant) and forced air-warming devices are recommended. Pulse oximetry of both upper and lower extremities will assist in detecting inadvertent ligation of the descending aorta. For patients with coexisting disease, intra-arterial pressure monitoring provides a method of assessing arterial blood gases, electrolytes, hematocrit, and acid-base status. Whether by cuff or arterial line, blood pressure should be monitored in both an upper and lower extremity and observed carefully before and after ductal occlusion. Proper ductal occlusion will typically be accompanied by an increase in diastolic blood pressure consistent with the elimination of pulmonary runoff. Significantly decreased or absent blood pressure in the lower extremity indicates aortic rather than ductal occlusion. A gradient between the systolic pressure in the upper and lower extremities indicates the creation of aortic coarctation.

Although inhaled anesthetics can be safely used for many patients undergoing PDA ligation, neonates are prone to hemodynamic instability with exposure to inhaled anesthetics and benefit from an intravenous anesthetic technique using opioids such as fentanyl and possibly a benzodiazepine along with muscle relaxation.

Neonatal PDA ligation is often performed in the newborn intensive care unit (ICU) to avoid the additional risks of transport, need for ventilator changes, and hypothermic exposure. High spinal anesthesia, caudal and thoracic epidural techniques have all been described as safe and producing faster recovery [26, 27].

Lung isolation improves surgical exposure, especially through VATS surgical techniques, but it may require ventilation with 100% inspired oxygen to maintain acceptable oxygenation. Prior to lung isolation, FiO_2 should be minimized and hypocarbia avoided in order to maintain pulmonary vascular tone and to limit the degree of left-to-right shunting. This technique is usually unnecessary for small infants, with either gentle retraction and packing in the case of open thoracotomy or gentle CO_2 insufflation with retraction for VATS, being sufficient.

Infants having thoracotomy or VATS often require postoperative mechanical ventilation, especially if they are premature. Older patients or patients undergoing transcatheter closure are often extubated at the conclusion of the case [17–27].

KEY POINTS: PATENT DUCTUS ARTERIOSUS

- PDA is a relatively common congenital heart defect and is associated with prematurity.
- Pathophysiology depends on the degree of shunting, which is greatest with a short ductus of large diameter.
- Surgical closure may involve an open, thoracoscopic, or transcatheter technique.
- Choice of anesthetic is unlimited in older, less symptomatic patients but often restricted to the opioid technique in premature infants.
- Monitoring perfusion above and below the ductus is critical in recognizing inadvertent ligation of the aorta.
- Immediate postoperative extubation is an option for healthy patients and/or transcatheter techniques, but postoperative mechanical ventilation is required for most neonates and infants.

Aortopulmonary window

Incidence, anatomy, and natural history

Aortopulmonary window (APW), also known as aortopulmonary (or aorticopulmonary) fistula, fenestration, or septal defect is a rare anomaly comprising approximately 0.1–0.6% of all congenital heart defects [28–30]. A total of 50–80% of patients with APW have associated defects including PDA (72%), a right pulmonary artery from the aorta (32%), anomalous origin of a coronary artery from the pulmonary artery (23%), VSD (20%), agenesis of the ductus arteriosus (20%), and other lesions [28, 31]. Embryologically, APW is thought to originate from nonfusion or malalignment of the aortopulmonary and truncal septi, or complete absence of the aortopulmonary septum [28, 32].

The basic anatomical defect in APW consists of a communication between the aorta and the pulmonary artery. Type I APW is a proximal defect located just above the sinus of Valsalva, a few millimeters above the semilunar valve. Type

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II is a distal APW located in the uppermost portion of the ascending aorta. Type III is a total defect involving the majority of the ascending aorta. Type IV or intermediate defects, which are neither proximal nor distal, are also designated in this system; these defects are noted for being conducive to device closure because of adequate superior and inferior rims (Figure 26.5) [33].

Uncorrected APW results in a reported 40% mortality in the first year of life, with a substantial proportion of survivors succumbing to CHF later in childhood [32].

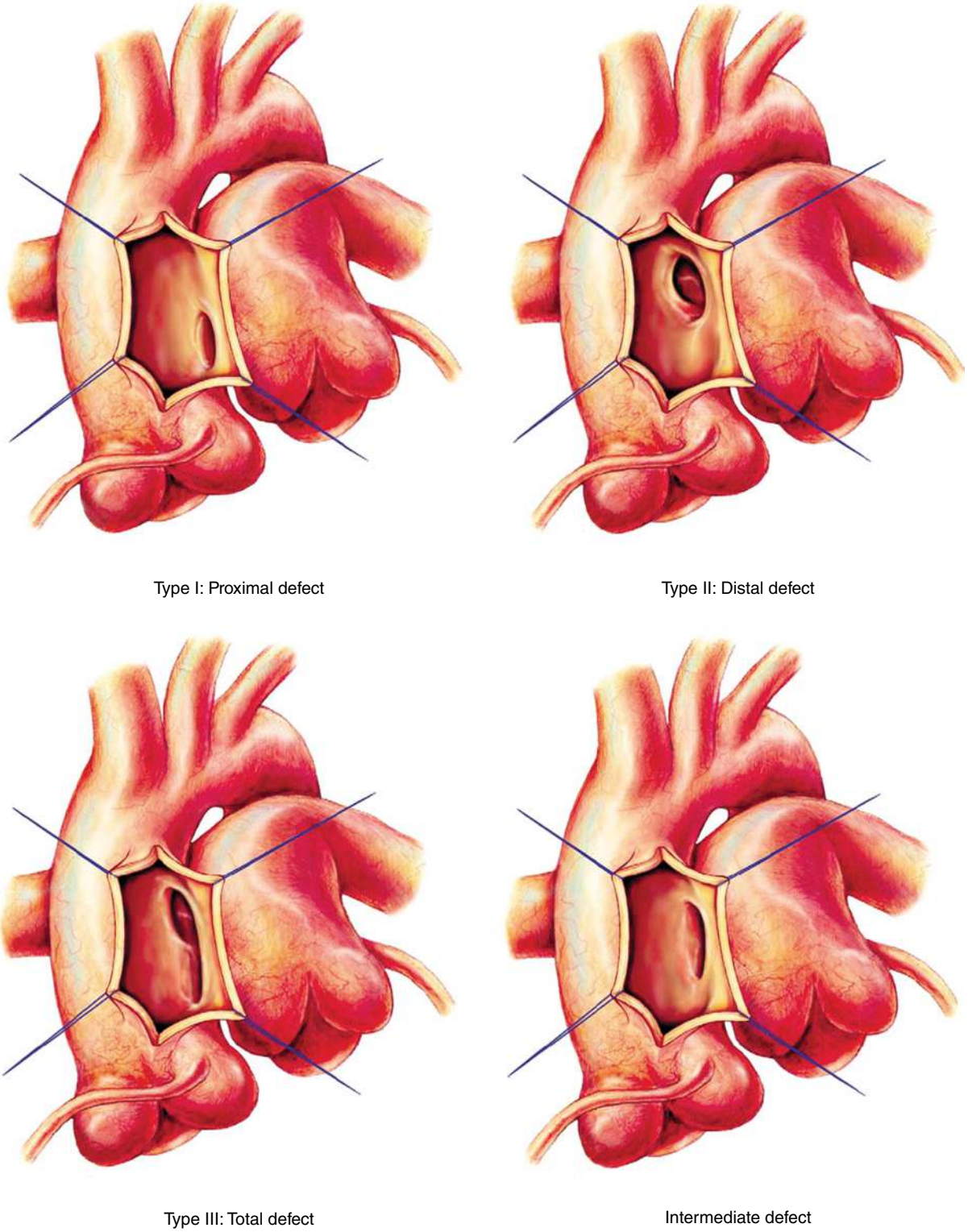


Figure 26.5 Classification of aortopulmonary window variants (see text for explanation). (Source: Backer [33]. Reproduced with permission of Elsevier.)

Pathophysiology

The pressure gradient between the aorta and pulmonary artery will produce significant left-to-right shunting depending on the size of the defect and the relative resistances of the pulmonary and systemic vascular beds. A defect such as an APW is considered "restrictive" when it is small enough that there is a size-related flow limitation across the defect indicated by a significant pressure gradient from one side to the other. Flow across a "non-restrictive" APW is not limited by size; any pressure gradient across the defect is related only to the relative resistances of the pulmonary and systemic vascular beds. Coexisting cardiac anomalies may alter the pathophysiology. Pulmonary hypertension can develop as early as 12 days of age [34].

Surgical and transcatheter approaches and outcomes

A variety of techniques have been described for repair of APW, including ligation and/or division with or without cardiopulmonary bypass, transaortic patch closure, complete separation, and reconstruction of both the aorta and pulmonary artery, and transcatheter closure [33, 35–37]. The repair is usually performed via median sternotomy with the use of cardiopulmonary bypass. Surgical repair of the aortic defect can be accomplished using a pulmonary artery flap with subsequent repair of the pulmonary artery with a pericardial patch [38, 39]. A Gore-Tex® cardiovascular patch can also be used to close the defect [33] (Figure 26.6). Care must be taken to explore and repair associated anomalies of the pulmonary and coronary arteries and to repair coexisting cardiac abnormalities. Deep hypothermia and circulatory arrest may be required for the repair of large APW involving the proximal ascending aorta in neonates.

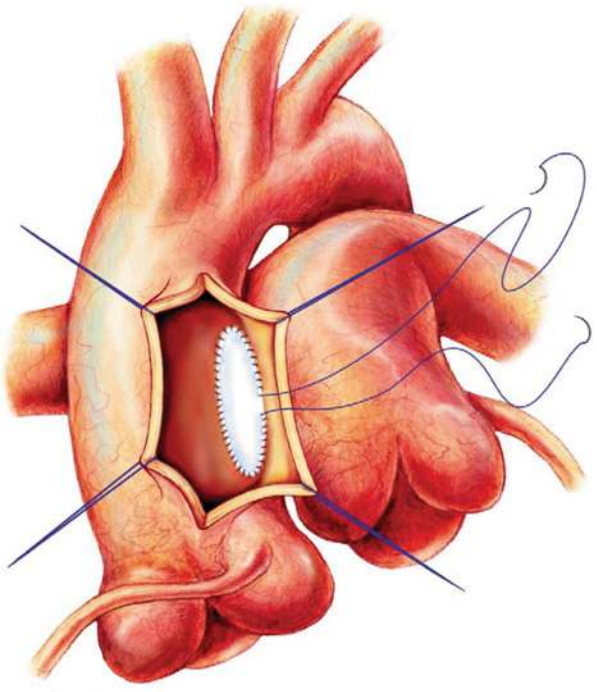


Figure 26.6 Patch closure of type III aortopulmonary window (APW) total defect. Aortic cross-clamp and cardiopulmonary bypass cannulas not shown (Source: Backer [33]. Reproduced with permission of Elsevier.)

Actuarial survival after repair of APW is between 80 and 100%, with the most significant risk factor in the modern era being the presence of associated cardiac defects. Simply repaired APW lesions have a mortality approaching zero [28]. Transcatheter closure of APW is typically accomplished with an umbrella-type occluding device [36, 37, 40–42]. Although transcatheter closure has generally been reserved for patients with restrictive defects, device closure has been reported in selected non-restrictive defects as well [43].

Anesthetic considerations

The anesthetic management of APW is similar to that of truncus arteriosus. Younger patients may have considerable diastolic runoff from low PVR. Prior to cardiopulmonary bypass, efforts should focus on maintaining pulmonary vascular tone. This can be accomplished by lowering the minute ventilation and restricting the FiO_2 to maintain a moderate hypercarbic respiratory acidosis and an oxygen saturation level of 80–85%. In these cases, surgical snaring of the pulmonary artery prior to bypass may also be helpful. In contrast, patients undergoing later repair are likely to present with elevated PVR, and anesthetic management should include avoiding further increases in PVR.

Regardless of PVR at presentation, all patients with APW are at risk to develop perioperative pulmonary hypertension. The administration of inhaled nitric oxide, as well as other maneuvers described above, may be necessary to lower PVR. Patients exhibiting signs of pulmonary hypertension should initially be maintained under deep sedation with or without neuromuscular blockade during the immediate postoperative periods (see Chapter 33).

KEY POINTS: AORTOPULMONARY WINDOW

- APW is a rare lesion with a pathophysiology and management scheme that varies with the size and location of the defect.
- Surgical and transcatheter approaches have been used; deep hypothermic bypass and circulatory arrest may be required.
- High pulmonary blood flow and diastolic runoff into the pulmonary circulation should be mitigated by maintaining PVR through a lower oxygen saturation and moderate hypercarbia.
- Pulmonary hypertension precautions should be observed in all patients with APW.

Atrial septal defects

Incidence

Atrial septal defects (ASDs) make up approximately 5–10% of all CHDs with the secundum ASD comprising nearly 80% of all ASDs. Isolated ASDs are more common in females than males by a factor of 2:1 [9]. A probe-patent foramen ovale is

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found in approximately 30% of otherwise normal adult hearts [44]. When associated with other CHDs, an ASD may be a life-saving communication allowing mixing of blood between the pulmonary and systemic circulations. Examples include total anomalous pulmonary venous return, tricuspid atresia, and transposition of the great arteries (TGA). In such cases, an ASD may be iatrogenically created as a palliative measure, often on an urgent or emergent basis (e.g. balloon atrial septostomy).

Anatomy

The right and left atria are normally divided by the fusion of two septa: the septum primum and the septum secundum. The septum primum develops during the fourth week of gestation and the septum secundum during the fifth week [7]. The septum primum originates posteriorly and advances across the atrial midline. The opening it leaves by incompletely advancing to the endocardial cushion is the ostium primum, which later closes. A second opening, the ostium secundum, forms in the central portion of the septum primum. The septum secundum originates anteriorly and to the right of the septum primum and advances over the ostium secundum. Although traditionally the septum secundum has been described in terms similar to those of the septum primum in its formation and composition, it is instead to a large extent composed of an infolding of the superior margin of the atrium rather than an advancing wall of tissue [45]. It eventually develops a central opening called the foramen ovale. The septum primum forms the valve of the foramen ovale on the left atrial side [7, 46]. Figure 26.7 illustrates the process of embryologic development of the atrial septum. Errors in this process form the basis for the five different types of ASDs: secundum, primum, sinus venosus, coronary sinus, and patent foramen ovale (PFO) (Figure 26.8) [48].

Secundum ASD

The secundum ASD is contained within the area bordered by the limbus of the fossa ovalis [49]. It results from abnormal reabsorption of the septum primum or defective formation or shortening of the septum secundum. Combinations of these abnormalities may contribute to large defects.

Primum ASD

The primum ASD results from abnormalities in the formation of the septum primum. It is frequently associated with atrioventricular canal (AVC) defects, especially partial atrioventricular canal (PAVCs) that include a cleft in the anterior leaflet of the left atrioventricular valve. AVC defects are due to abnormalities in the fusion of the endocardial cushions.

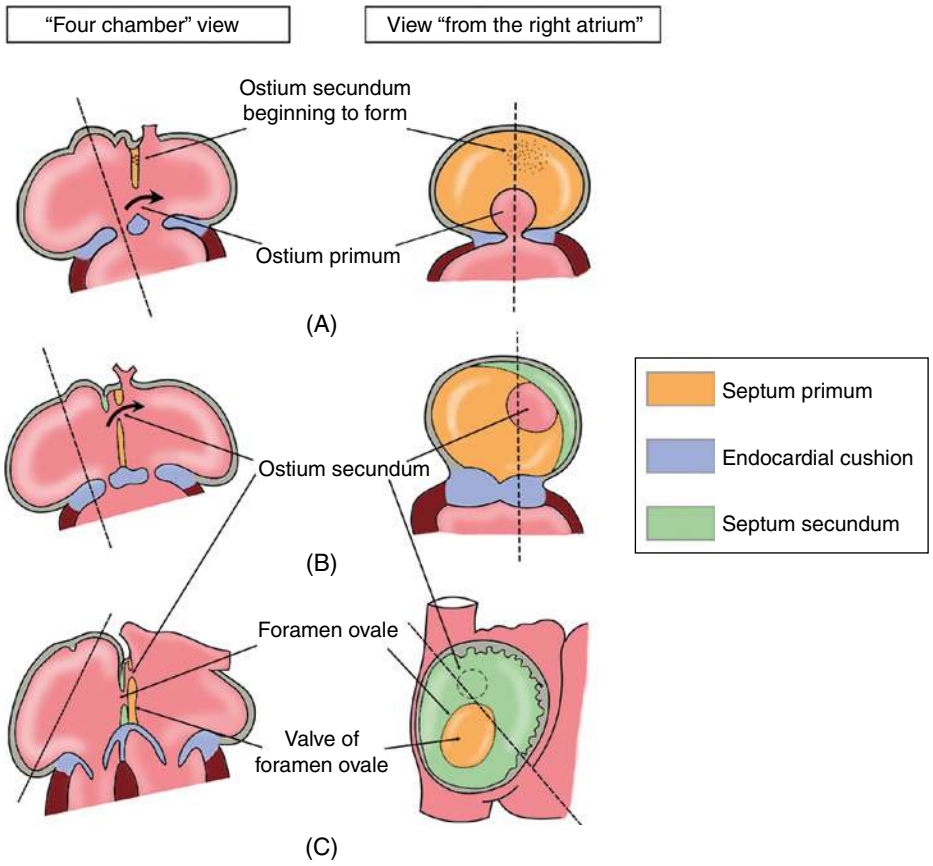


Figure 26.7 Embryologic development of the interatrial septum. The left column is a long axis cross-section similar to that of an echocardiographic four-chamber view. The right column is the view from the right atrium with the right atrial free wall removed, looking at the right side of the developing atrial septum. (A) 29 days gestation. (B) 37 days gestation. (C) Birth. (Source: Adapted from Radiologykey.com.)

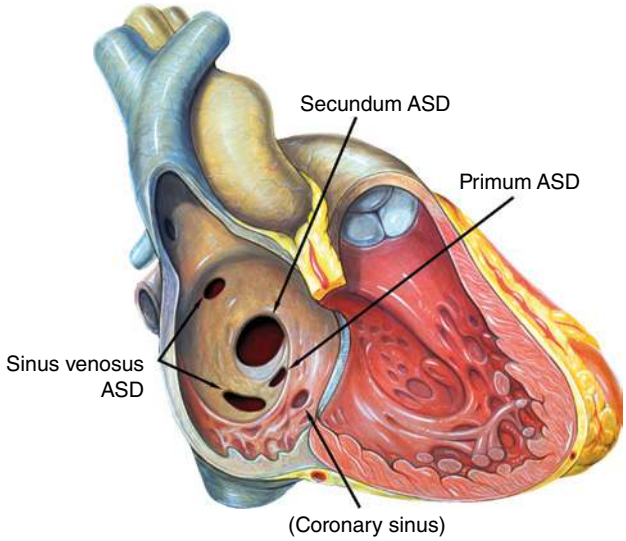


Figure 26.8 Types of atrial septal defects. Coronary sinus ASDs are not typically visible from the right atrium, as they result from unroofing of the coronary sinus as it courses along the posterior wall of the left atrium. Also not shown is the patent foramen ovale (PFO), which is usually covered by the remnant of the septum primum. (Source: Conti et al. [179]. Reproduced with permission of Elsevier.)

Sinus venosus ASD

Sinus venosus defects result from abnormal development of the septum secundum or the sinus venosus (the primitive venous collecting chamber). The most common type is located near the superior vena cava (SVC) orifice and is associated with partial anomalous pulmonary venous return involving the right upper and middle pulmonary veins. Defects near the orifice of the inferior vena cava (IVC) also exist and may involve partial anomalous pulmonary venous return of the right lower pulmonary vein.

Coronary sinus ASD

Coronary sinus ASD, also called an unroofed coronary sinus, results from an absence in the wall between the coronary sinus and the left atrium. This allows blood from the left atrium to drain into the right atrium via the coronary sinus. Persistent left SVC is also associated with this defect [49].

Patent foramen ovale

PFO results from failure of fusion of the septum primum to the limbus of the septum secundum. Patency of the foramen ovale is normal during fetal life and allows right-to-left shunting of blood in order to bypass the lungs in fetal circulation. Following birth, PVR decreases and SVR increases. Subsequent higher pressure in the left atrium causes the septum primum to close over the foramen ovale, but it may not completely fuse to the septum secundum.

Natural history

Isolated ASDs are usually asymptomatic during infancy and childhood despite the increased volume load on the right ventricle. CHF usually occurs after the second or third decade of life due to chronic right ventricular volume overload. Pulmonary hypertension can occur in up to 13% of unoperated patients younger than 10 years of age; however, progression to Eisenmenger syndrome is unusual [9]. The risk of arrhythmia is increased with increasing shunt volume and atrial dilation. Patients with a Qp : Qs of 2 : 1 or less have an 11% incidence of atrial arrhythmia, compared to 38% in those with Qp : Qs of 3 : 1 or greater [50]. An ASD is sometimes discovered during a neurological work-up for transient ischemic attacks or strokes from paradoxical emboli [49].

Pathophysiology

The amount of left-to-right shunting at the atrial level is dependent on two factors: the size of the defect and the relative compliance of the right and left ventricles. Shunting occurs primarily during diastole and produces a volume burden on the cardiovascular system that is proportionate to the degree of shunting.

Surgical and transcatheter approaches and outcomes

Surgical repair of an ASD is usually recommended between the ages of 3 and 5 years [51]. Spontaneous closure of small secundum type ASDs occurs in up to 87% of infants in the first year of life [9], and controversy exists regarding the closure of small ASDs that are asymptomatic. Conventional surgical treatment involves median sternotomy with the use of CPB to perform a primary repair or patch closure, with surgical mortality approaching 0% [9, 52]. Primum ASD repairs typically require patch closure as well as repair of the coexisting mitral valve cleft (Figure 26.9). Sinus venosus defects are usually repaired using a patch to close the ASD and baffle the anomalous pulmonary veins to the left atrium. The SVC may need to be translocated and anastomosed to the right atrial appendage to avoid baffle obstruction (Warden procedure). Many centers now favor partial sternotomy approaches because of the improved cosmetic result with similar morbidity and mortality to complete sternotomy [53–55]. Robotically assisted totally endoscopic ASD repair with remote access perfusion (using femoral cannulation) has been described in adults [56]. With conventional repair, postoperative dysrhythmias are reported in 23% of patients, and as many as 2% of patients may need a pacemaker following surgery [9].

Increased use of transcatheter ASD closure in the cardiac catheterization laboratory has dramatically reduced the number of operative repairs. While the several FDA-approved devices that have been utilized differ in detail, the typical design consists of a catheter-deployed expandable "double umbrella" type occluder, with a right and left atrial side (Figure 26.9) [57]. Nonsurgical transcatheter closure of PFO without an occluding device has also been described, using either radio frequency ablation or suture closure [58, 59]. Transcatheter ASD closure is usually performed under general anesthesia with the use of TEE to guide placement. However, intracardiac echocardiography using intravascular two-dimensional imaging may eliminate the need for TEE and reduce the need for general anesthesia [60]. Transcatheter closure is safe, associated with decreased hospital stay, lack of

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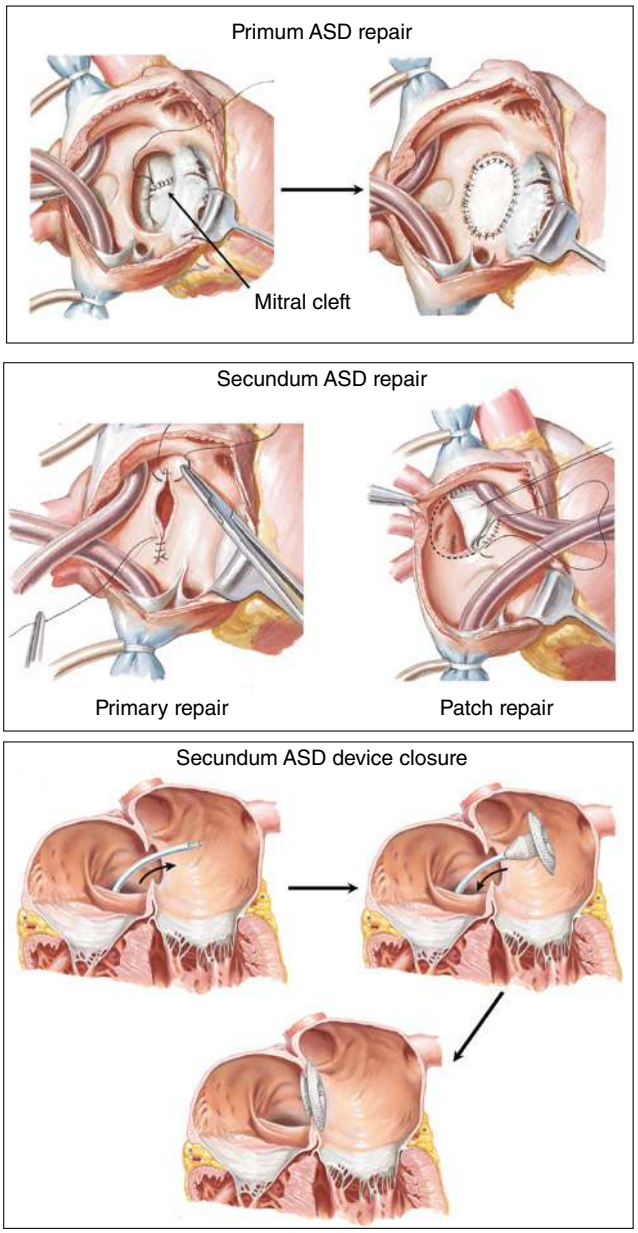


Figure 26.9 Surgical repair of primum (top) and secundum (middle) atrial septal defect (ASD), and device closure of secundum ASD (bottom). A primum ASD requires closure of the mitral valve cleft (top left), followed by patch closure of the ASD (top right). A secundum ASD may be repaired by direct suture closure (middle left) or by patch closure (middle right). Secundum ASD closure device is delivered via catheter across the ASD, wherein the left atrial side of the device is opened. The device is then pulled back against the ASD, where the right atrial side is opened and the device is deployed from the catheter. (Source: Conti et al. [47]. Reproduced with permission of Elsevier.)

a surgical scar, avoidance of CPB, and reduced anesthetic requirements. Limitations to transcatheter closure of ASD include patient size (introducer sheaths may be too large for smaller patients), type of ASD (usually limited to PFO or secundum), and the requirement for an adequate tissue rim to which the device can attach [61]. Occasionally, pre-procedure transthoracic echocardiography does not provide complete information about septal tissue rim size or other requirements for device closure, and backup surgical repair can be arranged during the same anesthetic if the TEE examination reveals contraindications to a transcatheter procedure.

Anesthetic considerations

Patients with an isolated ASD are generally asymptomatic and do not have pulmonary hypertension. Therefore, the induction of anesthesia can be safely accomplished with either inhalation or intravenous techniques. Whenever possible, patients should have an intraoperative TEE performed prior to incision, because transthoracic echocardiographic studies are sometimes unable to exclude the possibility of a partial anomalous pulmonary venous return due to difficulty in visualizing all four pulmonary veins. During surgery, TEE can be helpful to assess the de-airing of the left heart and adequacy of the repair. Most patients have a good myocardial function and do not require inotropic support perioperatively. Maintenance of anesthesia typically consists of a combination of inhaled and intravenous agents. Adjunct regional techniques are favored by some and may facilitate early extubation [62–65]. Tracheal extubation in the operating room (OR) has been shown to decrease patient charges without compromising patient care when compared to extubation in the ICU [66, 67]. Whatever technique is chosen, the primary goals for the uncomplicated ASD patient should include preparation for early extubation either in the OR or within the first 4 hours postoperatively.

KEY POINTS: ATRIAL SEPTAL DEFECT

- ASDs are a common congenital heart lesion and may be important in maintaining adequate intracardiac mixing in association with other life-threatening heart defects.
- Untreated ASDs may be asymptomatic until CHF, atrial arrhythmias, or strokes from paradoxical emboli occur, generally after the second or third decade of life.
- Anesthesia for isolated ASD closure is generally well tolerated and early extubation is an important goal.
- Transcatheter techniques for ASD closure have dramatically reduced the number of operative repairs.

Ventricular septal defects

Incidence

VSD is the most common CHD, occurring in 50% of all children with congenital heart disease and in 20% as an isolated lesion. The reported incidence ranges from 1.56 to 53.2/1,000 live births [68]. VSD is associated with a variety of inherited conditions, including trisomy 13, 18, and 21 as well as VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal, and limb anomalies) association and CHARGE (coloboma, heart defects, atresia choanal, retarded growth and development, and genital hypoplasia, and ear anomalies/deafness) syndrome [69].

Anatomy

Embryologically, the primitive left ventricle is formed from the ventricular portion of the bulbus cordis and the primitive right ventricle is formed from the proximal portion at approximately 23–25 days gestation. Disruption of ventricular septation at a given point during primary morphogenesis is responsible for four different types of VSD: type I: subarterial; type II: perimembranous; type III: inlet; and type IV: muscular (Figure 26.10) [69, 70]. Each of these types has various synonyms, making VSD nomenclature somewhat complex. A thorough understanding of the anatomy of the normal ventricular septum is helpful in making sense of the various types and subtypes of VSDs. In this way, VSDs may be understood as those within the muscular portion of the ventricular septum (type IV) and those that exist at its margins near the tricuspid and pulmonary valves (types I–III).

Type I: subarterial VSD

The subarterial (also called *juxtaarterial, subpulmonary, supracristal, conal*, or *infundibular*) VSD is located just beneath the pulmonary valve, within the outlet septum, above the crista supraventricularis. The crista supraventricularis defines the inferior margin of the smooth-walled muscular tube of tissue connecting the right ventricle to the pulmonary artery known as the *infundibulum* or *conus arteriosus*. As a result of the location of this defect, a Venturi effect may be produced by the jet of blood flowing through the VSD causing the right or noncoronary aortic cusp of the aortic valve to prolapse toward the defect, producing aortic insufficiency [68]. This type of lesion is more common among VSDs found in the Asian population, occurring in about 30% of all VSDs versus in about 5% of the non-Asian population [71].

Type II: perimembranous VSD

The perimembranous (also called *paramembranous* or *conoventricular*) VSD is a communication adjacent to a portion of the membranous septum and the fibrous trigone of the heart, where the aortic, mitral, and tricuspid valves are in fibrous continuity. These infracristal defects (below the crista supraventricularis) are the most common VSD subtype, accounting for approximately 80% of VSDs.

Type III: inlet VSD

Inlet VSDs (also called *canal type*) are located in the posterior region of the septum beneath the septal leaflet of the tricuspid valve. These defects account for approximately 10% of VSDs.

Type IV: muscular VSD

Muscular VSDs are located anywhere within the muscular portion of the interventricular septum. These defects can be multiple and represent approximately 2–7% of VSDs.

Natural history

Patients presenting with VSD may be asymptomatic or may exhibit signs and symptoms of CHF in varying degrees. The rate and extent of progression of symptomatology depend on the patient's age, size of the defect, and the degree of left-to-right shunting. Infants who have non-restrictive VSDs typically develop symptoms of CHF by 3 months of age because of the physiologic decline in PVR that occurs during early postnatal life. If left untreated, 15% of patients with large VSDs develop pulmonary hypertension that will progress to the development of pulmonary vascular obstructive disease, shunt reversal, and cyanosis

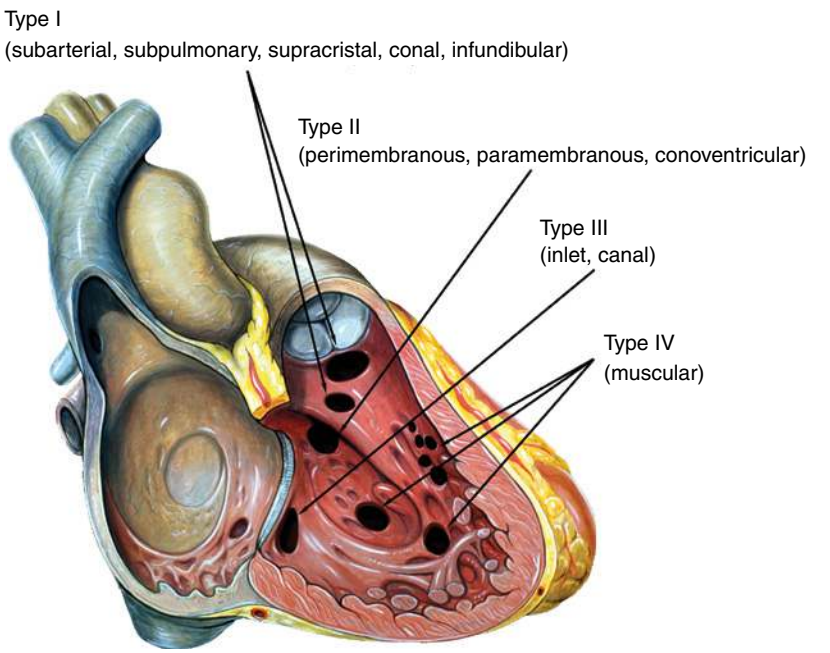


Figure 26.10 Types of the ventricular septal defect. (Source: Patrick J. Lynch, Medical Illustrator; C. Carl Jaffe, MD, Cardiologist / Wikimedia Commons / CC BY 2.5. https://commons.wikimedia.org/wiki/File:Heart_right_vsd.jpg.)

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(Eisenmenger syndrome) by the age of 20 years [72]. The irreversible changes that lead to Eisenmenger syndrome may develop by age 2 years; therefore it is important to close large non-restrictive VSDs within the first 2 years of life. However, these large defects often decrease in size over the first year, becoming restrictive and relatively asymptomatic, allowing avoidance of surgery through careful surveillance in some cases [73]. Spontaneous closure of small perimembranous and muscular VSDs occurs in as many as 50% of patients [72, 74, 75], and such patients are typically asymptomatic.

Pathophysiology

Isolated VSDs produce left-to-right shunting at the ventricular level, predominantly during systole. In contrast to ASDs, in which ventricular dilation is isolated to the right ventricle, the volume load induced by shunting through a VSD affects both ventricles. A VSD may be restrictive or non-restrictive, depending on size. A clear definition of a non-restrictive defect is elusive. The presence of a pressure gradient across the defect is inadequate because a gradient generally exists even in non-restrictive lesions related to the relative resistances of the pulmonary and systemic vascular beds. Proposed definitions involve the cross-sectional ratio of the defect to the aortic orifice, defect size versus body surface area, or shunt flow velocity [6].

In addition to the pathophysiology associated with left-to-right shunting, VSDs may be associated with secondary structural cardiac anomalies not related to the shunt and resultant volume loading. An example is the aortic valve prolapse often associated with VSDs near the aortic valve, resulting in aortic insufficiency. Another is the phenomenon of a "double-chambered right ventricle", which occurs with some frequency in the setting of a VSD. In this lesion, mid-cavity obstruction by hypertrophied muscle bands creates a high-pressure proximal chamber and a low-pressure distal chamber within the right ventricle. These lesions are also often associated with discrete subaortic stenosis [76].

Surgical and transcatheter approaches and outcomes

Surgical repair of VSD is usually by patch closure and occasionally by primary closure using CPB via median sternotomy. Perimembranous and inlet VSDs are most commonly repaired via a right atriotomy, which may require detachment of the septal leaflet of the tricuspid valve for exposure [77] (Figure 26.11). Subarterial VSDs are most commonly repaired via the transpulmonary approach. Midmuscular VSDs are most commonly repaired via right atriotomy, and anterior or apical muscular VSD may be approached using right ventriculotomy. However, the use of a right ventriculotomy carries the risks of conduction disturbances and ventricular dysfunction later in life. Symptomatic patients with lesions that are not approachable via right atriotomy may be treated with pulmonary artery banding until the patient is larger, allowing transatrial repair. Pulmonary artery banding is also utilized for multiple muscular VSDs and in patients that are high-risk candidates for CPB. Partial median sternotomies, as well as small right anterolateral thoracotomies, are advocated by some because of improved cosmetic results [78, 79]. Total thoracoscopic repair has also been described [80].

Timing for surgical repair varies depending on age at presentation and severity of signs and symptoms. Patients younger than 6 months of age are repaired if they manifest uncontrollable CHF and failure to thrive. Patients between 6 and 24 months of age undergo repair to treat CHF symptoms or pulmonary hypertension. Patients older than 24 months undergo repair if the Qp : Qs is greater than 2:1. Among patients with subarterial VSD, the presence of aortic insufficiency is an indication for surgical repair to prevent further progression of the valvular insufficiency [81, 82]. A defect

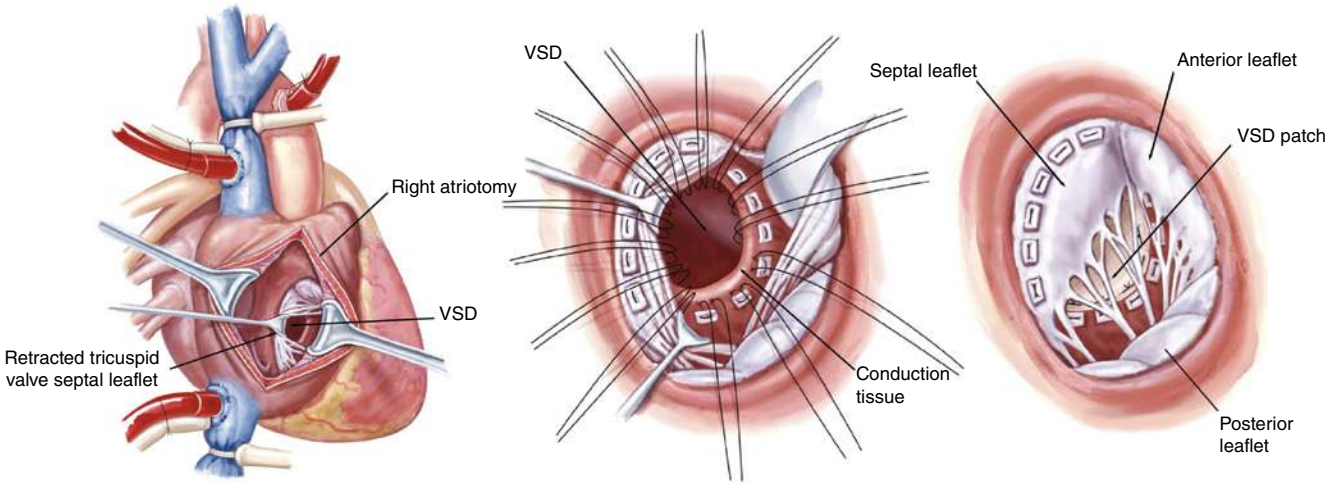


Figure 26.11 Surgical repair of perimembranous ventricular septal defect (VSD). This technique, typically done through a right atriotomy, is similar to that for inlet VSD. Note exposure requires retraction or detachment of the septal leaflet of the tricuspid valve (Source: Conti et al. [47]. Reproduced with permission of Elsevier.)

size of greater than 5 mm is repaired to avoid progression to aortic cusp prolapse and aortic insufficiency, and defects less than 5 mm can be managed conservatively [83]. Finally, even small, otherwise asymptomatic VSDs are usually repaired because of the low risk of infective endocarditis.

Mortality for uncomplicated VSD in older patients is less than 1–2% [84]. Mortality for VSD repair in infants during the first year of life is less than 5% [85].

Transcatheter closure of VSDs has been performed successfully since at least the late 1980s [86–90]. Indications for use of these devices include all types of muscular VSDs, including apical and multiple, as well as perimembranous VSDs. Transcatheter closure is typically performed in the catheterization laboratory via percutaneous access. However, "hybrid" techniques involving a sternotomy to place a device either by direct visualization on CPB or in a beating heart using perventricular transcatheter placement have also been described [91]. The major limitation in the application of percutaneous transcatheter techniques is related to the size of the sheaths necessary for device delivery, precluding use in infancy. Complications of device closure include the need for blood transfusion, tricuspid valve regurgitation, and device embolization [86, 87]. Heart block is a particular concern following device closure of perimembranous VSDs, sometimes occurring years after placement [92–94].

Anesthetic considerations

Anesthetic management for patients with VSD is similar to that of ASD. Pulmonary hypertension may develop early, especially in patients with trisomy 21, and preoperative chest radiograph revealing decreased pulmonary vascular markings is indicative of pulmonary hypertension [95–99]. Such patients may respond to the use of inhaled nitric oxide prior to the termination of CPB and/or in the postoperative period. Right heart failure with decreased cardiac output may result if pulmonary hypertension is not controlled, and it may require the use of dopamine, milrinone, dobutamine, or isoproterenol.

Conduction disturbances may be transient or permanent. Atrioventricular heart block, formerly reported to occur in up to 10% of patients post-VSD repair, is now a rare complication occurring in less than 1% of patients after VSD closure [100]. If heart block develops, treatment with atrioventricular synchronous pacing using temporary pacing wires is indicated. Junctional ectopic tachycardia is sometimes observed in patients younger than 1 year after surgery for lesions that involve VSD repair, most commonly after tetralogy of Fallot correction. Treatment includes cooling to 35 °C, increasing anesthetic depth, paralysis, procainamide, esmolol, or amiodarone [101].

Intraoperative use of TEE will allow recognition of residual VSDs and intracardiac air, as well as provide an assessment of ventricular volume and function. Small muscular VSDs often become apparent after the closure of larger VSDs. Frequently these smaller defects, especially if near the apex, may not be amenable to surgical repair or worth the risk of returning to CPB.

Patients with uncomplicated VSDs are good candidates for extubation in the OR or early after arrival in the ICU.

KEY POINTS: VENTRICULAR SEPTAL DEFECT

- VSDs are the most common congenital heart defects.
- Both ventricles are affected by left-to-right shunting through a VSD.
- The pulmonary vascular tone should be maintained in those patients with pulmonary overcirculation prior to repair.
- Be prepared to treat arrhythmias, including heart block and junctional ectopic tachycardia, especially after repair.
- Patients with uncomplicated VSDs should be considered for early extubation.

Atrioventricular canal

Incidence

Four to 5% of CHDs involve defects of the atrioventricular septum, and AVC defects occur in 0.19 in 1,000 live births [99, 102]. AVC is associated with multiple syndromes and occurs in approximately 20% of persons with trisomy 21. It accounts for 15% of congenital heart defects in persons with Noonan syndrome and nearly 50% in persons with Ellis–van Creveld syndrome [103].

Anatomy

Atrioventricular canal defects result from failure of the endocardial cushions to fuse during the fifth week of fetal development [7]. AVC consists of three basic defects: (i) an ostium primum defect resulting in interatrial communication, (ii) abnormal atrioventricular valves, and (iii) an inlet VSD resulting in an interventricular communication. Three types of AVC exist: (i) partial, (ii) transitional, and (iii) complete [104].

Partial AVC

The PAVC defect consists of an ostium primum ASD and a cleft in the anterior leaflet of the mitral valve, usually resulting in some degree of insufficiency [96]. The tricuspid valve is often abnormal as well, and no VSD or other interventricular communication exists.

Transitional AVC

The transitional (also called *intermediate*) atrioventricular canal (TAVC) defect consists of an ostium primum ASD, abnormal atrioventricular valves that form two separate orifices, and a VSD, often restrictive, just below the atrioventricular valves [104]. Like the PAVC defect, the left atrioventricular valve is usually associated with a cleft and has some degree of insufficiency.

Complete AVC

The complete atrioventricular canal (CAVC) defect consists of an ostium primum ASD and a non-restrictive VSD just below a common atrioventricular valve that bridges both the right and

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left sides of the heart to create a single valve orifice [105]. The left atrioventricular portion of the valve usually contains a cleft that is insufficient. Three classifications of CAVC defects exist based on the chordal attachments of the anterior bridging leaflet of the common atrioventricular valve and are commonly referred to as Rastelli types A, B, and C [104, 105] (Figure 26.12).

In Rastelli type A CAVC, which is the most common type, the anterior bridging leaflet is divided at the septum into right and left components and attached to the crest of the ventricular septum by thin chordae tendinae. Rastelli type B CAVC is rare and is characterized by anomalous papillary muscle attachment from the right side of the ventricular septum to the left side of the anterior bridging leaflet. Rastelli type C CAVC is defined by an anterior leaflet that lacks any ventricular septal attachments and "floats" above the septum [104]. The Rastelli type C defect may be associated with other major cardiac or extracardiac anomalies such as tetralogy of Fallot or trisomy 21 [49].

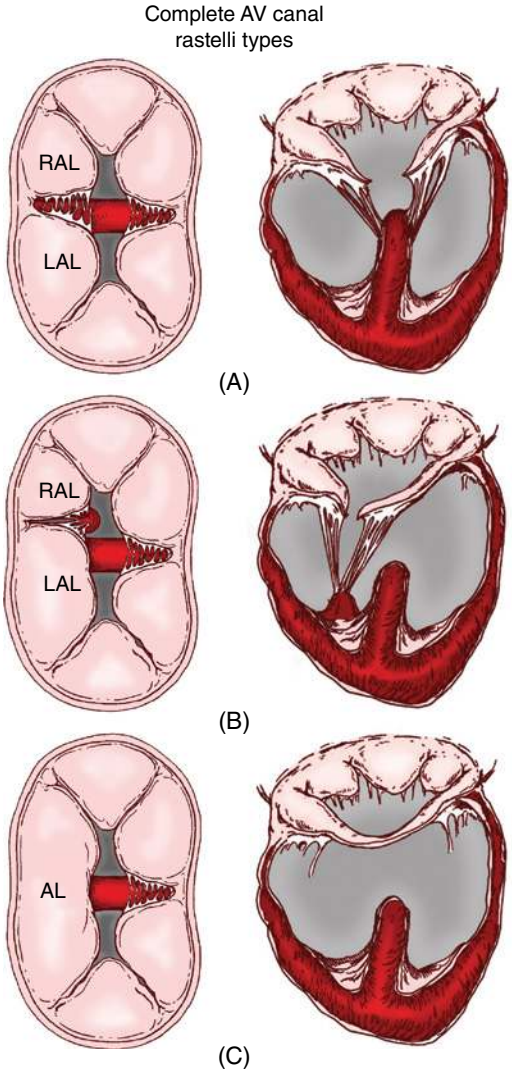


Figure 26.12 Complete atrioventricular canal defects: Rastelli types A, B, and C. LAL, left anterior leaflet; RAL, right anterior leaflet. (Sources: Jacobs et al. [104]. Reproduced with permission of Elsevier; Munoz et al. [105]. Reproduced with permission of Springer Nature.)

Other variants of AVC also exist, including right or left ventricular dominant types in which the common atrioventricular valve opens predominantly into one of the ventricles ("unbalanced" AVC). If one ventricle is hypoplastic the physiology produced by such lesions is similar to other single ventricle lesions (see Chapter 30 for a detailed presentation). Many lesions occur in association with AVC, including PDA, Tetralogy of Fallot, coarctation of the aorta, subaortic stenosis, left SVC, asplenia, and polysplenia syndromes [105].

Natural history

As with other left-to-right shunts, pulmonary hypertension may develop by 1 year of age and eventually lead to Eisenmenger syndrome [106]. The severity of CHF and symptoms will depend on the degree of left-to-right shunting and the severity of atrioventricular valve regurgitation. Among the forms of AVC, PAVC is the least symptomatic, CAVC the most, and TAVC intermediate. Patients with untreated PAVC may do well through childhood but have an increased likelihood of developing CHF in adulthood, especially as atrial dysrhythmias develop [49]. The presence of moderate to severe atrioventricular valve regurgitation leads to earlier development of CHF and higher morbidity and mortality if untreated. Those patients with PAVC presenting with CHF in the first year of life should be suspected of having additional lesions, most commonly left-sided obstructive lesions [107]. Patients with CAVC develop CHF, failure-to-thrive, and frequent respiratory infections in the first year of life. During this same interval, 12% of these children will develop irreversible pulmonary hypertension. Those with trisomy 21 develop pulmonary hypertension earlier and with increased severity as compared to other children; however, this has not manifested as a risk factor in surgical repair or long-term outcome [96–98, 108–110].

Pathophysiology

A left-to-right shunt may occur at the atrial, ventricular, and atrioventricular valvar level, depending on the type of AVC present. This shunting, in addition to atrioventricular valve regurgitation, results in volume overload of both the atria and ventricles. Volume overload soon develops into CHF and may result in pulmonary hypertension as the ratio of pulmonary to systemic blood flow increases.

Surgical approaches and outcomes

Surgical repair of PAVC is usually performed at age 2–5 years unless there are signs of CHF or other lesions that necessitate earlier repair. Patients with TAVC may be relatively asymptomatic and may tolerate surgical repair at an older age.

Primary complete surgical repair for patients with CAVC is performed between 1 and 6 months of age because it is safe, controls CHF, prevents the development of fixed pulmonary hypertension, and reduces annular dilation (a cause of atrioventricular valvar regurgitation) [107, 111, 112].

Surgical techniques vary, but generally consist of a right atriotomy with patch closure of the ASD, cleft closure in the anterior leaflet of the left atrioventricular valve, and closure of the VSD with a patch or, in the case of the TAVC,

pledgetted sutures [49, 111]. A one- or two-patch technique can be used. The one-patch technique consists of a single patch closure of both the ASD and VSD (Figure 26.13) [113, 114]. Staged repair with initial pulmonary artery banding is reserved for cases of severe respiratory illness, sepsis, or anatomy not suitable for biventricular repair. The presence of associated cardiac anomalies such as Tetralogy of Fallot, double outlet right ventricle (DORV), left-sided obstructive lesions, and unbalanced AVC (with a hypoplastic ventricle) further complicates the repair and results in higher mortality, especially in patients with a hypoplastic ventricle [115, 116].

Mortality for the repair of PAVC is less than 5%, and the mortality for the complete repair of CAVC is between 2.5 and 10.5% [112, 117–119]. The presence of preoperative pulmonary hypertension and increasing size of the VSD is

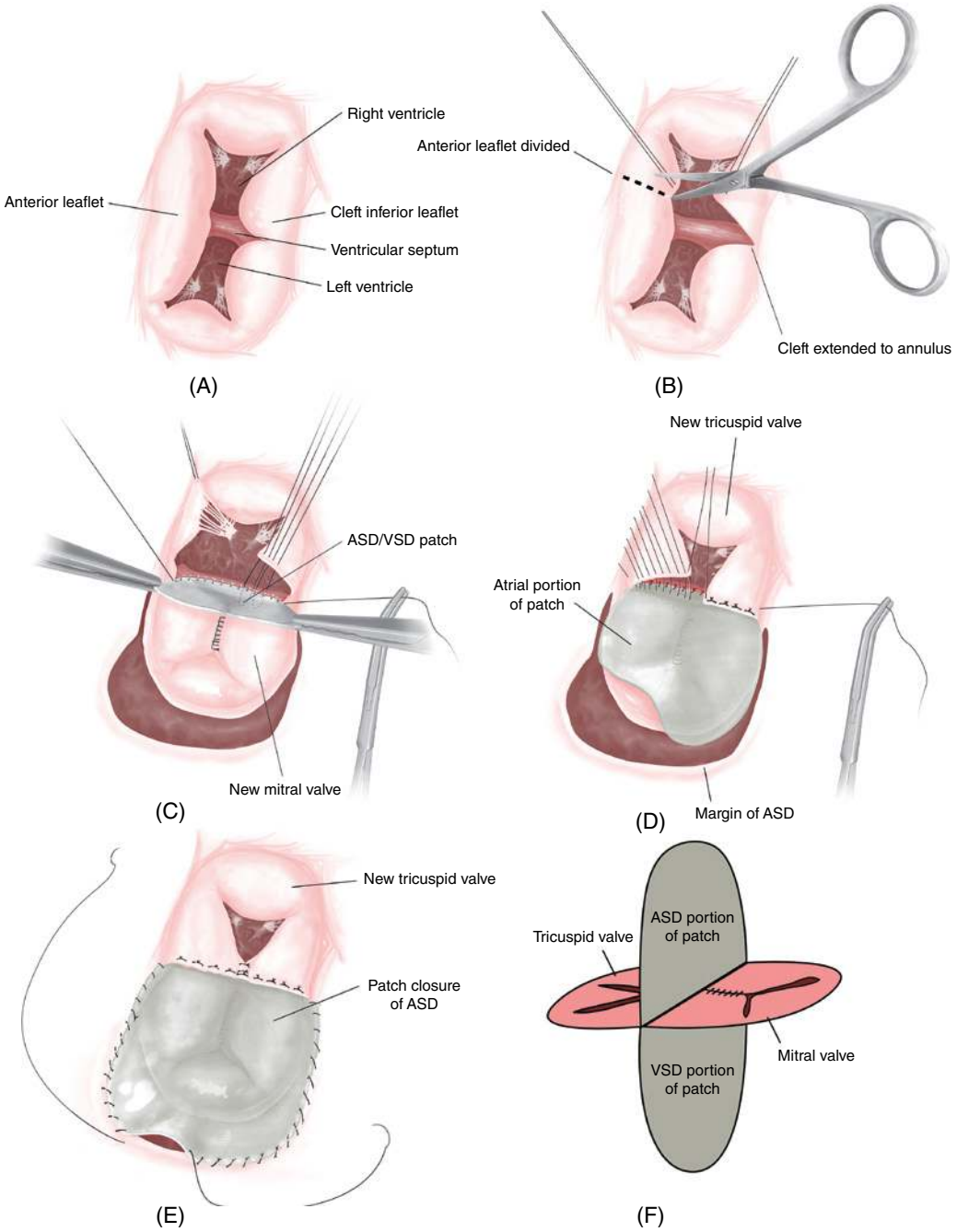


Figure 26.13 One-patch repair of a complete atrioventricular canal (AVC) defect. (A) The defect is exposed. (B) The anterior and posterior common valve leaflets are divided to separate the mitral and tricuspid sections. (C) The VSD is closed using the inferior portion of the patch. The mitral valve is rendered bicuspid by the closure of the anterior and posterior common leaflets on the mitral side, which had been natively separate, to create a functional mitral valve after being anchored to the patch. (D) The tricuspid valve leaflets are anchored to the mid-portion of the patch. (E) The superior portion of the patch is used to close the atrial septal defect. (F) Schematic representation of the completed repair, showing the position of the patch and the newly created tricuspid and mitral valves. ASD, atrial septal defect; VSD, ventricular septal defect. (Source: Razzouk et al. [113]. Reproduced with permission of Elsevier.)

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associated with higher morbidity and mortality among patients undergoing complete repair of CAVC [49, 117].

Anesthetic considerations

Anesthetic management of AVC defects depends primarily on the degree of left-to-right shunting and the presence and severity of pulmonary vascular hypertension. As with other septal defects, balancing the ratio of PVR to SVR and thereby limiting the amount of pulmonary overcirculation is paramount to successful management, and is usually accomplished by manipulations in FiO_2 and ventilation (see above). TEE is very helpful in detecting residual intracardiac shunts, assessing atrioventricular valvar function, and determining ventricular function and volume following repair.

Surgical placement of left atrial and pulmonary arterial pressure lines may be used to guide the management of inotropes, use of inhaled nitric oxide, and volume replacement. Persistent elevation and acute increases in pulmonary arterial pressure contribute to right heart failure and increased mortality [117]. Pulmonary hypertension develops commonly in these patients and is treated with hyperventilation, 100% oxygen, systemic alkalinization, opioids, and inhaled nitric oxide. Increasing the pH is more effective than lowering the $PaCO_2$ in controlling pulmonary pressures and may be accomplished by the administration of sodium bicarbonate [120]. Sildenafil has also been effective in this setting [121].

Most patients require inotropic support upon weaning from CPB, and those with residual atrioventricular valve regurgitation and/or VSD benefit from the use of milrinone or other afterload reduction. Hypotensive patients who have elevated left atrial pressures should be evaluated for the presence of severe residual left atrioventricular valve regurgitation or stenosis, residual VSD, left ventricular outflow tract obstruction, or left ventricular dysfunction. Intraoperative TEE is essential for the initial diagnosis of these conditions, and re-initiation of CPB and repair may be necessary.

CAVC repair is associated with conduction abnormalities, especially atrioventricular and sinoatrial nodal dysfunction resulting in complete heart block. In this situation, atrioventricular sequential pacing is necessary to minimize atrioventricular valve regurgitation and to improve cardiac output [105].

KEY POINTS: ATRIOVENTRICULAR CANAL

- AVC is associated with trisomy 21, Noonan syndrome, and Ellis–van Creveld syndrome
- AVC may be partial, transitional, or complete
- Measures to maintain pulmonary vascular tone are necessary to avoid pulmonary overcirculation prior to repair
- Following bypass, pulmonary hypertension is common and therapy may include inhaled nitric oxide, hyperventilation, 100% oxygen, systemic alkalinization, deep sedation, and neuromuscular blockade
- Inotropic support is often needed post-bypass
- Residual defects and cardiac function are evaluated by TEE post-repair
- Dysrhythmias, including complete heart block, are common and temporary pacing may be required

Double outlet right ventricle

Incidence

DORV comprises approximately 1–1.5% of all patients with congenital heart disease with an incidence estimated at 1/10,000 live births [122]. Although DORV can occur with an intact ventricular septum, this is extremely rare [123]; almost all patients with DORV also have a VSD.

Anatomy

DORV is a type of ventriculoarterial connection in which both great vessels arise either entirely or predominantly from the right ventricle. This definition is intended to simplify what is in fact a complex spectrum of defects ranging from morphology that mimics tetralogy of Fallot to that which resembles transposition of the great vessels. Embryologically, DORV is a bulboventricular malformation that results from failure of proper alignment of the conotruncus with the ventricular septum [122].

Characterization of the anatomy of DORV is crucial in understanding the physiologic consequences as well in determining the surgical approach for palliation or correction. Complete characterization of the anatomy will include (i) the relationship of the VSD to the great arteries, (ii) the relationship of the great arteries with respect to one another, (iii) the morphology of the ventricles and their outflow tracts, and (iv) the presence of associated anomalies [123]. Four different anatomic types of DORV are defined on the basis of the relationship of the VSD to the great arteries: (i) subaortic VSD, (ii) subpulmonary VSD, (iii) doubly committed VSD, and (iv) noncommitted VSD [124, 125] (Figure 26.14).

DORV with subaortic VSD

These lesions represent approximately 51–56% of DORV [123, 126] and are characterized by a VSD located beneath the aortic valve. The great vessels may be normally related or transposed. When this defect is associated with pulmonary stenosis, the resulting physiology is similar to that of tetralogy of Fallot [122].

DORV with subpulmonary VSD

DORV with subpulmonary VSD represents approximately 30% of DORV [126, 127]. Pulmonary stenosis is rare, but subaortic or aortic arch obstructions are common. The VSD is typically non-restrictive. This lesion often occurs in the form of the *Taussig–Bing* type, with D-malposition of the great arteries in the absence of pulmonary stenosis [122]. The resulting physiology is similar to that of transposition of the great arteries.

DORV with doubly committed VSD

Three to 10% of patients with DORV have a doubly committed VSD [126–128]. The doubly committed VSD results from hypoplasia of the conal septum and variable degrees of override of the VSD by both great arteries [122].

DORV with noncommitted VSD

Twelve to 17% of patients with DORV have a noncommitted VSD [123, 126], and the VSD is an apical

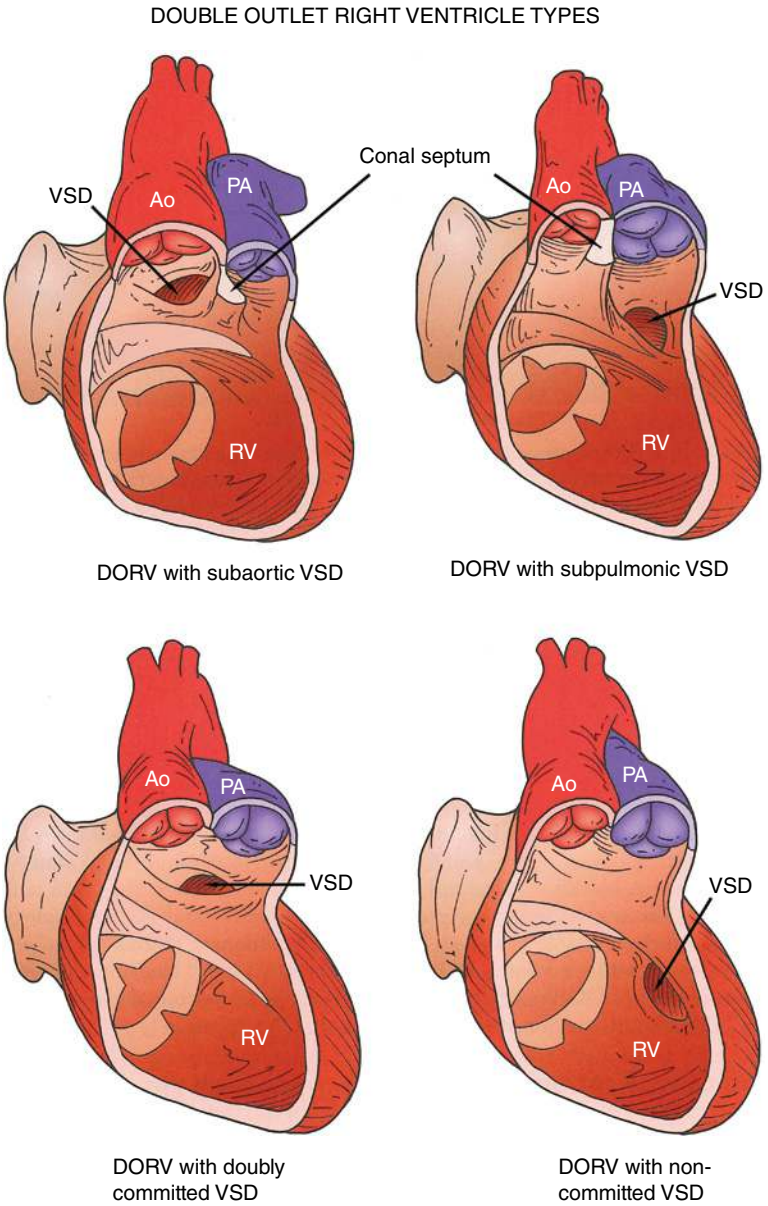


Figure 26.14 Anatomic sub-types of double outlet right ventricle (DORV), as determined by the position of the ventricular septal defect. Ao, aorta; PA, pulmonary artery; RV, right ventricle; VSD, ventricular septal defect. (Source: Ungerleider et al. [125]. Reproduced with permission of Elsevier.)

muscular or membranous-inlet type. The VSD is remote from the great arteries and is frequently associated with AVC defects [122].

Natural history and pathophysiology

The natural history and pathophysiology of DORV are dependent on the specific anatomy of the lesion and relative amounts of pulmonary versus aortic blood flow as well as the degree of mixing of pulmonary and systemic venous blood. Consideration of these variables serves to simplify the pathophysiology of DORV into three basic subtypes: VSD, Tetralogy of Fallot, and transposition of the great arteries [129].

DORV with a doubly committed or subaortic VSD without pulmonary stenosis produces physiology similar to that of a VSD. Because VSDs in this setting are usually non-restrictive, the degree of left-to-right shunting will generally depend on the relative ratio of PVR to SVR.

DORV associated with pulmonary stenosis resembles the physiology of tetralogy of Fallot with varying degrees of cyanosis depending on the severity of pulmonic stenosis. These patients have right-to-left shunting across the VSD and may have hypercyanotic spells, erythrocytosis, and failure to thrive. Although there is a fixed component of obstruction, pulmonary blood flow may vary due to alterations in PVR. Pulmonary stenosis is present in approximately 50% of patients with DORV [122].

DORV with a subpulmonary VSD without pulmonary stenosis usually produces physiology similar to transposition of the great arteries. Streaming of pulmonary venous blood to

the pulmonary artery and systemic venous blood toward the aorta results in variable degrees of mixing of oxygenated and deoxygenated blood. Patients can present early with both cyanosis and CHF followed by the development of pulmonary vascular occlusive disease if left untreated.

DORV may be associated with other anomalies that further affect pathophysiology, such as multiple VSDs, AVC defects, PDA, aortic arch obstruction, interrupted aortic arch, subaortic stenosis, hypoplastic ventricle, or mitral valve abnormalities [126–132].

Surgical approaches and outcomes

The surgical approach to DORV varies depending on the type of DORV and the associated anomalies, and the preoperative delineation of anatomy is crucial to determine the operative strategy. However, echocardiography, angiography, and magnetic resonance imaging may still result in incomplete information due to the complexity and anatomic variations of this lesion [131, 133]. Three-dimensional reconstruction using computed tomography and 3D printing can delineate complex anatomy and facilitate surgical planning (Figure 26.15) [134, 135]. Depending on the lesion, four surgical treatment options generally exist: (i) palliative procedures such as Blalock–Taussig shunts, coarctation repairs, and pulmonary artery banding; (ii) intraventricular repair with a baffle from the left ventricle to the aorta [125, 136] (Figure 26.16); (iii) intraventricular baffle from the left ventricle to the pulmonary artery followed by the arterial switch; and (iv) bidirectional cavopulmonary shunt staged to the Fontan procedure (univentricular heart repair) [126–132].

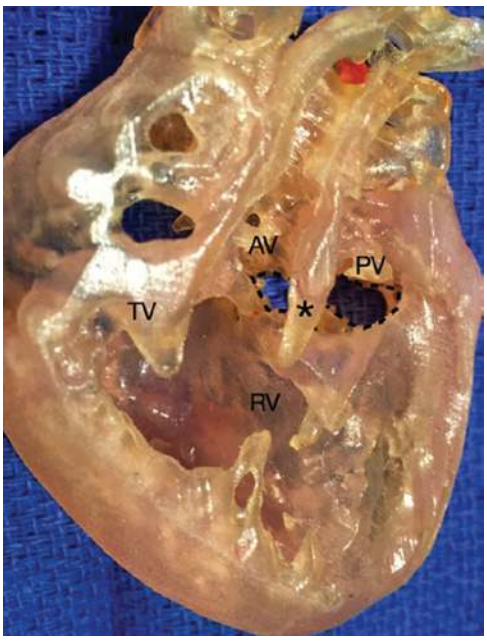


Figure 26.15 A coronal plane three-dimensional flexible polyjet-printed model of a heart with the right ventricle free wall removed. This model is from a heart with a double outlet right ventricle and doubly committed ventricular septal defect, which is outlined by the black dashed line. (Source: Bahtla et al. [134]. Reproduced with permission of John Wiley & Sons.)

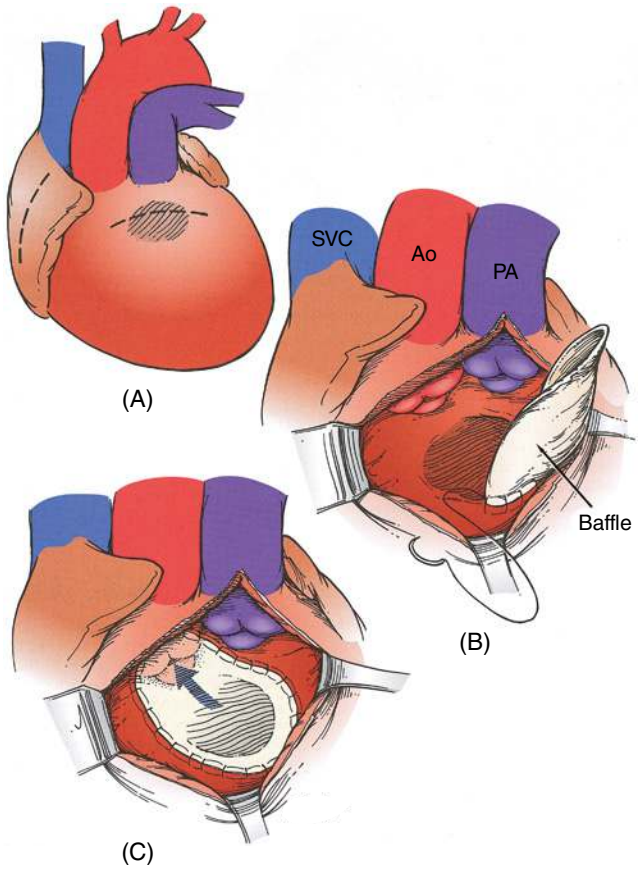


Figure 26.16 Surgical repair of double outlet right ventricle without pulmonary stenosis. (A) The approach can be either by right atriotomy or ventriculotomy (dashed lines). (B and C) A baffle is used to close the ventricular septal defect and direct blood from the left ventricle to the aorta without obstructing flow from the right ventricle to the pulmonary artery. (Source: Ungerleider et al. [125]. Reproduced with permission of Elsevier.)

The overall early mortality for the repair of DORV is approximately 9% [126, 127, 132]. Ten-year survival is 81–86% [126, 127]. Significant risk factors for early mortality include congenital mitral valve anomalies, side-by-side great arteries, multiple VSDs, and age at operation <1 month [126–130]. Among patients with complex anatomy, Fontan palliation may be the procedure of choice as it has been associated with lower early mortality in this group compared to biventricular repair [126].

Anesthetic considerations

Anesthetic management varies greatly depending on the specific type of DORV and associated anomalies. Management of palliative procedures, such as the modified Blalock–Taussig shunt, is reviewed in Chapter 28. Patients with pulmonary stenosis who present with physiology similar to tetralogy of Fallot should be managed to minimize right-to-left shunting (see Chapter 28). Patients with subpulmonary VSD without pulmonary stenosis who have physiology similar to TGA should be managed as such (see Chapter 29). Subaortic and noncommitted VSDs without

pulmonary stenosis produce physiology similar to that of a VSD and should be managed as described earlier in this chapter. Patients with complex DORV and other associated anomalies that proceed through the single ventricle staged palliation to the Fontan procedure are reviewed in Chapter 30. In all patients with DORV, regardless of specific anatomy, intracardiac shunting must be balanced with manipulation of PVR and SVR to optimize systemic cardiac output and oxygen delivery.

Arrhythmias are common, especially with repairs involving baffling and enlargement of the VSD. Ventricular tachyarrhythmias and complete heart block can occur in as many as 9% of patients postoperatively and may require permanent pacing [123, 126, 127]. Frequently, repair of DORV is complex and requires periods of circulatory arrest. Patients may have residual VSDs, valvar insufficiency, outflow tract obstruction, or ventricular dysfunction. Postoperative TEE and left atrial pressure monitoring are helpful in determining the diagnosis and guiding management.

KEY POINTS: DOUBLE OUTLET RIGHT VENTRICLE

- The four anatomic sub-types of DORV depend on the location of the VSD: subaortic, subpulmonary, doubly committed, and noncommitted
- DORV with a doubly committed or noncommitted VSD is managed as a VSD
- DORV associated with pulmonary stenosis is managed similarly to tetralogy of Fallot
- DORV with subpulmonary VSD without pulmonary stenosis is managed similarly to transposition of the great vessels
- Some patients require single ventricle staging to a Fontan
- Postoperative arrhythmias are common
- Inotropic support is often needed, especially after long bypass intervals

Truncus arteriosus

Incidence

Truncus arteriosus is an uncommon congenital heart defect representing less than 3% of all congenital heart defects [137–139]. Deletion of chromosome 22q11 is present in approximately 11–35% of patients with truncus arteriosus, and this chromosomal abnormality is associated with DiGeorge and velocardiofacial syndromes. Patients with these syndromes also have noncardiac anomalies such as aplasia or hypoplasia of the thymus and/or parathyroid glands, which can lead to T-cell deficiency and/or hypocalcemia. Patients may also have palatal abnormalities, speech and learning disabilities, neuropsychological disorders, and craniofacial dysmorphia [140–142]. As many as 77% of patients with 22q11 deletion are immunocompromised [142].

Anatomy

Truncus arteriosus is defined by the presence of a single great artery arising from the base of the heart that supplies the coronary, pulmonary, and systemic circulations. Embryologically, this defect results from the failure of the truncus arteriosus to divide into the aorta and pulmonary artery.

Truncus arteriosus has historically been classified by two main systems. The first and most widely used classification system was described by Collett and Edwards in 1949 and the second by Van Praagh and Van Praagh in 1965 [143, 144]. The Collett and Edwards classification is based on the embryologic arrested development of the pulmonary arteries from the sixth aortic arches and is categorized into four different subtypes. For the purpose of this chapter, the Collett and Edwards system will be used (Figure 26.17) [143, 144].

Type I truncus arteriosus

Type I truncus arteriosus accounts for 70% of truncus arteriosus lesions. It is defined by the origin of the main pulmonary artery from the truncus dividing into left and right pulmonary arteries.

Type II truncus arteriosus

Type II truncus arteriosus accounts for 30% and is defined by the separate origin of the left and right pulmonary arteries from the posterior surface of the truncus, with the branch pulmonary arteries arising very close to one another.

Type III truncus arteriosus

Type III truncus arteriosus is also characterized by separate origin of the left and right pulmonary arteries, but in this

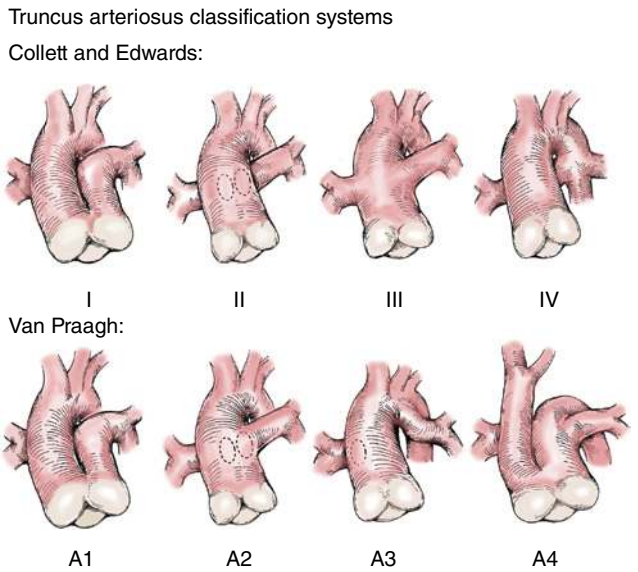


Figure 26.17 Major classification systems for truncus arteriosus. The "A" in the Van Praagh system indicates the presence of a ventricular septal defect (rare cases of the intact ventricular septum are designated with a "B"). The Collett and Edwards system is used for the purposes of this chapter. (Source: Jacobs et al. [104]. Reproduced with permission of Elsevier.)

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case, the arteries arise from the lateral aspects of the truncus and are widely separated. This type accounts for approximately 1% of cases.

Type IV truncus arteriosus

Type IV is included for historical purposes but has been rejected as a true form of truncus arteriosus. It is now defined as a form of pulmonary atresia and VSD and is sometimes called "pseudotruncus." There is a complete absence of the pulmonary arteries in this defect, with bronchial and collateral arteries of the descending aorta providing the blood supply to the lungs.

Truncus arteriosus is most commonly associated with a VSD but can occur with an intact ventricular septum. The truncal valve may be dysplastic and may have an abnormal number of leaflets, varying between two and six [144]. Truncal valve insufficiency is estimated to occur in 25–50% of patients; varying degrees of truncal valve stenosis may also occur [144]. Anomalies of the coronary arteries may also exist. Additionally, truncus arteriosus is associated with other cardiac anomalies such as aortic arch obstruction, ASDs (62%), right aortic arch (21–36%), aortic arch interruption (11–19%), PDA (18%), aberrant subclavian artery (4–10%), absence of one pulmonary artery (10%), and persistent left SVC (4–9%) [137, 139].

Natural history

If left untreated, the early CHF and increased pulmonary blood flow associated with truncus arteriosus lead to the rapid development of pulmonary vascular occlusive disease in infancy. Patients without surgical treatment have a 74–100% mortality in the first year of life [133, 136, 137]. Surgical repair in patients older than 2 years is contraindicated when pulmonary vascular resistance (PVR) is greater than eight Wood units or when Eisenmenger syndrome is present [137].

Pathophysiology

Truncus arteriosus by definition has a common arterial trunk that provides blood flow to the coronary, pulmonary, and systemic arteries. As PVR falls in the early neonatal period, pulmonary blood flow progressively increases and results in CHF. A variable degree of mixing of the systemic and pulmonary venous blood occurs at the ventricular level through the VSD. The large runoff provided by the pulmonary arteries results in low diastolic pressures, which may be worsened by the presence of truncal valve insufficiency. Low diastolic pressures in the face of increased myocardial work and increased ventricular pressures place the patient at risk of developing myocardial ischemia from coronary steal.

Surgical and transcatheter approaches and outcomes

Definitive surgical repair is usually recommended in the neonatal period, although some centers time surgery on an individual basis, performing repair between 2 and 3 months of age [137–139, 145]. Early repair is indicated due to the rapid development of pulmonary hypertension and high mortality rate in patients in the first year of life if left untreated. Palliative surgery involving pulmonary artery banding has largely been abandoned except for those very few patients who are not suitable candidates for definitive repair [139]. Definitive surgical repair involves removal of the pulmonary arteries from the truncal root and closing the resulting defect either primarily or with a patch. The VSD is usually closed with a patch via a transatrial or transventricular approach. A right ventricle to pulmonary artery connection is provided by a valved homograft (Figure 26.18) [146]. Though direct anastomosis of the pulmonary artery with the right ventricle has been described, it may distort the pulmonary arterial architecture [147]. If high right ventricular

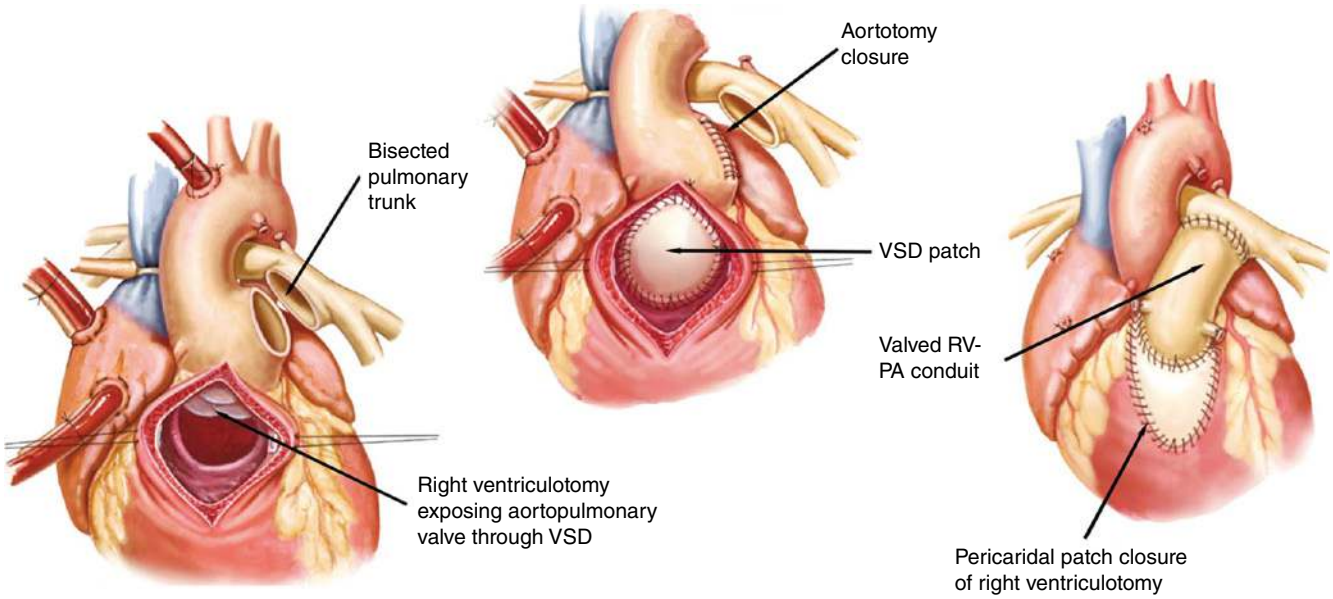


Figure 26.18 Surgical repair of a type I truncus arteriosus. A right ventriculotomy allows patching of the ventricular septal defect and placement of a valved conduit from the right ventricle to the bisected pulmonary artery trunk. (Source: Conti et al. [47]. Reproduced with permission of Elsevier.)

pressures are anticipated, a small ASD may be created as a "pop-off" for right-to-left shunting in order to improve cardiac output at the expense of arterial oxygen saturation [137, 138, 145, 148]. This ASD creation can be closed at a later date by a transcatheter technique in the cardiac catheterization laboratory. Moderate to severe truncal valve regurgitation is repaired by valvuloplasty, "double-homograft" technique with coronary reimplantation, or mechanical valve implantation [137, 149, 150]. Valve repair has been successful even in neonates and avoids or delays serial truncal valve replacements [150]. Over time, the right ventricular to pulmonary artery conduit may become stenotic and/or regurgitant. This may necessitate repair or replacement either surgically or via percutaneous techniques using a transcatheter pulmonary valve [151]. Much of the long-term pathophysiology after repair of truncus arteriosus is related to truncal valve dysfunction, particularly insufficiency. This contributes to the diminished physical health status of many of these patients in the second decade of life and beyond and may influence anesthetic management for later cardiac or non-cardiac surgery [152]. Early mortality after repair of truncus arteriosus is 5–18% [137, 138, 145, 148], and mortality rates are higher in infants who weigh less than 3 kg or have other cardiac anomalies [138, 148, 153].

Anesthetic considerations

Anesthetic management is dependent on the patient's anatomy and age at presentation. Depending on the severity of CHF, the patient may require preoperative inotropic support, and the induction of anesthesia should be accomplished with drugs that maintain SVR and preserve myocardial function. Ketamine or etomidate, often combined with fentanyl and/or midazolam, may be used to safely attain this goal. If an inhalational induction with sevoflurane is chosen, it should be performed with careful titration and extreme caution. Muscle relaxation may be achieved with any choice of a nondepolarizing neuromuscular blocking agent. Maintenance of anesthesia often includes high-dose fentanyl. Efforts to balance PVR and SVR to make the ratio of Qp : Qs approach 1:1 are essential. Care must be taken to avoid hyperventilation and excessive oxygenation, which lower PVR and may exacerbate pulmonary overcirculation and decrease diastolic blood pressure. Patients with truncal valve insufficiency combined with excessive pulmonary blood runoff will be particularly susceptible to myocardial ischemia, and it may be necessary for the surgeon to temporarily place a vessel snare around the pulmonary artery to limit pulmonary blood flow and increase diastolic blood pressure in the prebypass period. Occasionally this myocardial ischemia is heralded by ventricular fibrillation prior to bypass, and the anesthetic and surgical teams must be alert to this possibility and be prepared to intervene with external or internal defibrillation, open or closed cardiac massage, or emergent institution of bypass. Preoperative placement of external adhesive defibrillator pads is advisable. Those patients presenting late in infancy who have developed significant pulmonary hypertension from long-standing pulmonary overcirculation may require increased FiO_2 to maintain oxygen saturations between 80 and 90%. Unless ruled out by a chromosomal evaluation, patients with truncus arteriosus should be assumed to have DiGeorge syndrome and given irradiated blood products due to the high incidence of associated T-cell deficiencies. An absent or hypoplastic thymus is often evident upon sternotomy. Upon weaning from CPB, most patients require inotropic support, afterload reduction, ventricular volume assessment, and efforts to minimize pulmonary arterial pressures in order to improve right heart function.

Pulmonary hypertension is commonly present after cardiopulmonary bypass. These patients have signs of right heart failure with high central venous pressures, desaturation, tachycardia, hypotension, acidosis, and oliguria. Management includes hyperventilation, 100% oxygen, correction of acidosis, and inhaled nitric oxide as needed. These patients are usually kept heavily sedated for at least 24 hours postoperatively to minimize early pulmonary hypertensive crises. Signs similar to right ventricular dysfunction may also occur from residual VSDs or truncal valve stenosis or regurgitation. VSD closure or right ventricular incision may produce complete right bundle branch block, complete heart block (3–5%), junctional ectopic tachycardia, atrial tachycardias, or atrioventricular block in the postoperative period [82]. After bypass, many patients benefit from calcium infusions because of the hypocalcemia associated with DiGeorge syndrome and citrate binding of ionized calcium from the administration of blood products.

KEY POINTS: TRUNCUS ARTERIOSUS

- TA is associated with DiGeorge and velocardiofacial syndromes.
- Subtypes are defined by the relationship of the pulmonary arteries to the truncus.
- The presence of DiGeorge syndrome may necessitate calcium infusions and irradiated blood products.
- Pulmonary overcirculation requires maintenance of PVR pre-bypass and pulmonary hypertension precautions post-bypass.
- Myocardial ischemia may occur due to coronary steal as PVR decreases in the first weeks of life.
- Inotropic support is often necessary perioperatively.

Partial and total anomalous pulmonary venous return

Incidence

Both partial anomalous pulmonary venous return (PAPVR) and total anomalous pulmonary venous return (TAPVR) are rare cardiac lesions. Since PAPVR is often asymptomatic, its true incidence is unclear, but it has been reported as an incidental finding on autopsy in approximately 0.6% of the general population [154]. TAPVR represents less than 5% of congenital heart lesions [155–157].

Both PAPVR and TAPVR can be associated with other cardiac lesions. PAPVR is most commonly associated with sinus venosus type ASDs. Congenital mitral stenosis, DORV, VSD, tetralogy of Fallot, coarctation of the aorta, and PDA have all been described with PAPVR [156]. Nearly 33% of patients

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with TAPVR have other cardiac anomalies, such as CAVC, hypoplastic left heart syndrome or other single ventricle lesions, PDA, and transposition of the great arteries. Abnormalities of the atrial and visceral situs with heterotaxy syndrome, asplenia, and polysplenia are also common among patients with TAPVR [156]. Scimitar syndrome consists of either partial or complete anomalous drainage of the right pulmonary veins to the IVC, dextrocardia, and hypoplasia of the right lung. In these patients, the descending vertical vein resembles a scimitar, or Turkish sword, on a frontal chest radiograph [156].

Anatomy

Partial anomalous pulmonary venous return (PAPVR) is an anomaly in which some, but not all, of the pulmonary veins, connect to the right atrium or to one or more of its venous tributaries. In TAPVR, all of the pulmonary veins connect anomalously to the right atrium. Although these lesions are sometimes referred to as anomalous pulmonary venous *connections*, the use of the term *return* recognizes the fact that the pulmonary veins may be connected normally to the left atrium, but have an ASD anatomically configured to cause an abnormal return to the right atrium [154]. In either case, the pathophysiology is that of a left-to-right shunt.

The stage in embryologic development during which errors occur determines the various anatomic subtypes of abnormal pulmonary venous return. At 27–30 days of gestation, the pulmonary veins are derived from the splanchnic plexus that communicates with the cardinal and umbilicovitelline system of veins. Anomalous drainage to the left common cardinal system results in pulmonary venous connections to the coronary sinus or left innominate vein. Drainage to the right common cardinal system results in pulmonary venous connections to the SVC and/or the azygous vein. Drainage to the umbilicovitelline system results in pulmonary venous connection to the portal vein, ductus venous, or IVC. Early atresia of the common pulmonary vein, while primitive pulmonary–systemic venous connections are still present, results in TAPVR. If only the right or left portion of the common pulmonary vein becomes atretic, the persistence of the primitive pulmonary venous–systemic venous connection on that side leads to PAPVR [156].

Partial anomalous pulmonary venous return

Multiple types of PAPVR exist. The most common is the connection of the right pulmonary veins to the right SVC or right atrium which represents approximately 74% of patients. The next most common type is the connection of the right pulmonary veins to the IVC. The least common type is the connection of the left pulmonary veins to the left innominate vein or to the coronary sinus [156].

Total anomalous pulmonary venous return

Four different types of TAPVR exist based on the location of the anomalous connection: supracardiac, cardiac, infracardiac, and mixed (Figure 26.19) [158, 159]. A "stretched PFO" (70–80%) or true ASD (20–30%) is usually present in TAPVR.

Supracardiac TAPVR

Supracardiac connection comprises approximately 55% of cases of TAPVR. In this type, pulmonary venous drainage is to the SVC. In the most common form of this lesion, the two pulmonary veins from each lung converge posteriorly to the left atrium. A vertical vein then arises from the left side of the confluence and usually passes anterior to the left pulmonary artery and the left mainstem bronchus to drain into the left innominate vein, which then drains to the SVC. Pulmonary venous obstruction is unusual but may occur as a result of either intrinsic narrowing or extrinsic compression of the vertical vein. Although anomalous connection can occur to the SVC via a right-sided vertical vein, this is much less common [156]. A stretched PFO or ASD is present to allow left heart filling; although this constitutes a right-to-left shunt, cyanosis is often mild due to the greater degree of left-to-right shunting.

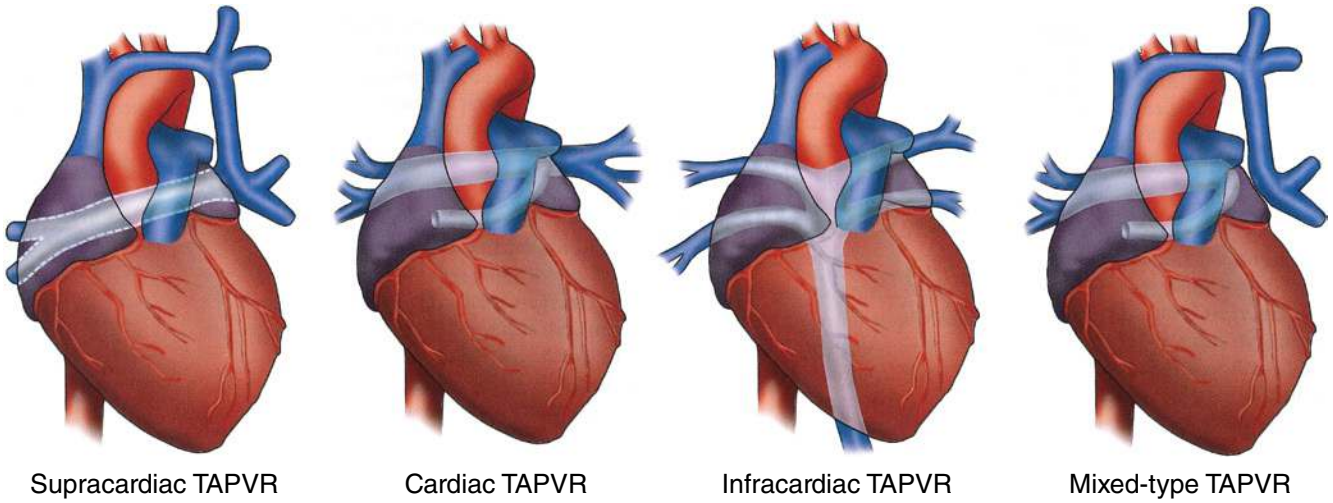


Figure 26.19 Four major subtypes of total anomalous pulmonary venous return (TAPVR) (see text for further explanation). (Source: Yuh et al. [158]. Reproduced with permission of McGraw Hill.)

Cardiac TAPVR

The cardiac type of TAPVR accounts for approximately 30% of cases. The pulmonary veins in this type drain into the coronary sinus or right atrium. Obstruction to the pulmonary veins was reported in 22% of patients in a series of TAPVR to the coronary sinus [160]. The coronary sinus is often "unroofed" prior to its drainage into the right atrium, allowing some pulmonary venous drainage into the left atrium; an ASD is usually present.

Infracardiac TAPVR

Infracardiac TAPVR comprises approximately 13% of cases and is commonly referred to as infradiaphragmatic TAPVR [156]. This type of connection usually involves a confluence of pulmonary veins from both lungs posterior to the left atrium. A descending vein then courses anterior to the esophagus through the diaphragm at the esophageal hiatus [161]. In 70–80% of patients, the descending vein then joins the portal venous system at either the splenic or the confluence of the splenic and superior mesenteric veins [161]. Nearly all patients with infracardiac TAPVR have obstructed pulmonary veins. This obstruction, which may be either intrinsic or extrinsic, can occur at any location along the pulmonary venous pathway. A stretched PFO or ASD is present in essentially all of these patients.

Mixed TAPVR

Mixed type TAPVR makes up approximately 2% of cases. This type of TAPVR consists of anomalous connections at two or more levels. The most common connection involves the left pulmonary veins draining into the left innominate vein and the right pulmonary veins draining to the right atrium or the coronary sinus [156]. Pulmonary venous obstruction has also been observed in these types of connections. A stretched PFO or ASD is usually present in this lesion.

Natural history and pathophysiology

Partial anomalous pulmonary venous return

PAPVR results in a variable amount of left-to-right shunting that depends on several factors: the number of anomalously draining veins as a percentage of the total pulmonary venous return, the pulmonary lobes or segments from which the anomalous veins originate, the relative resistances of the normally and anomalously drained pulmonary vascular beds, and the compliance of the receiving chambers. The left-to-right shunt leads to increased pulmonary blood flow and enlargement of the right atrium and ventricle as well as dilation of the pulmonary artery [156]. Most patients with an isolated single vein PAPVR and intact atrial septum are asymptomatic and have a normal life expectancy even if left untreated. Those patients with greater than 50% of the pulmonary veins draining anomalously or those with an associated ASD usually remain relatively asymptomatic until the third to fourth decades of life, when progressive symptoms of dyspnea, recurrent bronchitis, hemoptysis, chest pain, and palpitations with supraventricular arrhythmias can occur. These patients may also present with right heart failure or with pulmonary hypertension and cor pulmonale [156].

Total anomalous pulmonary venous return

The natural history and pathophysiology of TAPVR depend largely on whether or not pulmonary venous return is obstructed. In the presence of obstructed pulmonary veins, pulmonary venous hypertension exists with associated pulmonary edema. It is commonly confused with intrinsic lung disease when a chest radiograph reveals bilateral infiltrates in the absence of cardiomegaly. Occasionally neonates with hypoxemic respiratory failure placed on extracorporeal membrane oxygenation are subsequently diagnosed with obstructed TAPVR. Pulmonary arteriolar vasoconstriction occurs as a compensatory mechanism to minimize pulmonary edema. As PVR increases, the right ventricular systolic and end-diastolic pressures increase resulting in increased right atrial pressure and right-to-left shunting at the atrial level. Progressive systemic hypoxemia ensues with metabolic acidosis and multisystem organ failure. Left untreated, death occurs in the first few months of life [156].

In unobstructed TAPVR, the left-to-right shunt of pulmonary venous blood results in right atrial and ventricular enlargement with pulmonary overcirculation and subsequent right heart failure. The presence or absence of restrictive interatrial communication is another major determinant in the pathophysiology of TAPVR; 70–80% of infants have only a PFO, which restricts filling of the left atrium and ventricle. This causes tremendous pulmonary overcirculation, right-sided dilation, and minimal left-sided filling, which results in decreased size of the left atrium and ventricle. The abnormal displacement of the interventricular septum along with chronic underfilling of the left ventricle leads to decreased systemic cardiac output. Symptomatic CHF usually develops in the second month of life and may be partially or totally relieved by transvenous balloon atrial septostomy. Patients with a nonrestrictive interatrial communication, generally consisting of a secundum type ASD, have a large left-to-right shunt with increased pulmonary blood flow, but if left untreated may not develop signs of right heart failure or pulmonary hypertension until the third or fourth decade of life [156, 162].

Surgical approaches and outcomes

The timing of surgical repair of PAPVR is dependent in part on symptomatology. Patients with a single anomalous pulmonary vein with an intact atrial septum may never require surgical treatment. Surgical therapy is generally reserved for those patients with (i) hemodynamically significant left-to-right shunting with Qp : Qs greater than 2:1; (ii) patients with recurrent pulmonary infections, especially those associated with Scimitar syndrome; (iii) patients having surgical repair of other major cardiac lesions; and (iv) patients with anomalous connections which affect surrounding structures by compression or obstruction [156]. Surgical technique for repair of PAPVR varies depending on the specific anatomy present. The repair can consist of a direct anastomosis of the anomalous veins to the left atrium, or more commonly an

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indirect communication may be developed utilizing a patch to baffle the anomalous veins to the left atrium while closing the ASD with the same patch. In configurations where the SVC is at risk for obstruction, it may be transected above the anomalous pulmonary veins and translocated to the right atrial appendage (Warden procedure). In cases of PAPVR in which there is a dual connection to the right and left atrium, which often presents as a connection to the right atrium via a vertical vein and to the left atrium as a "dormant" pulmonary vein, the anomalous connection (e.g. vertical vein) can be occluded via transcatheter techniques [163].

Obstructed TAPVR should be corrected emergently at the time of diagnosis [164]. Patients with unobstructed TAPVR with restrictive interatrial communications are urgently palliated with blade and/or balloon atrial septostomies. These patients (and those with unobstructed TAPVR and nonrestrictive interatrial communications) can be medically managed for elective surgical repair, usually in the first year of life.

Techniques for surgical repair of TAPVR depend on the specific anatomy involved. In some cases, a period of deep hypothermic circulatory arrest may be necessary. Surgical repair generally includes incision and enlargement of the anomalous pulmonary venous confluence and direct anastomosis with the left atrium [165]. Occasionally, a patch is needed to baffle the veins to the left atrium, particularly with cardiac-type defects with drainage to the coronary sinus. So-called "sutureless" techniques are intended to reduce the risk of acquired pulmonary vein stenosis by using marsupialization of pericardium or pleura to create the atrial anastomosis [166, 167]. Examples of surgical techniques employed based on TAPVR type are illustrated in Figure 26.20 [168].

Operative mortality for the repair of asymptomatic PAPVR approaches zero [169], and in older symptomatic patients has been reported as less than 6% [170]. Operative mortality for patients with TAPVR is somewhat higher, between 7 and 9% [171–173]. Risk factors for operative mortality in TAPVR include heterotaxy syndrome and single ventricle [171, 174].

Anesthetic considerations

Intraoperative considerations for patients with PAPVR are similar to the management of ASD. Minimizing pulmonary blood flow by control of ventilation and consideration for early extubation following repair should be the primary goals.

The prebypass management of the patient with obstructed TAPVR generally includes maximizing PaO_2 with ventilatory support which may include significant levels of positive end-expiratory pressure (PEEP), inspiratory pressures, and FiO_2, avoiding metabolic acidosis, and maintaining hemodynamic stability with the use of inotropic medications as necessary. Pre-bypass inhaled nitric oxide is contraindicated because the pulmonary arteriolar dilation and increased pulmonary blood flow in the face of a fixed distal anatomic obstruction will worsen pulmonary mechanics and often paradoxically worsen hypoxemia. TEE should be employed with caution due to the risk of further compression and obstruction to pulmonary veins even in the presence of nonobstructed TAPVR. Perioperative monitoring of central venous, left atrial, and pulmonary arterial pressures is helpful.

After bypass, inhaled nitric oxide should be used empirically in the case of obstructed TAPVR and should be readily

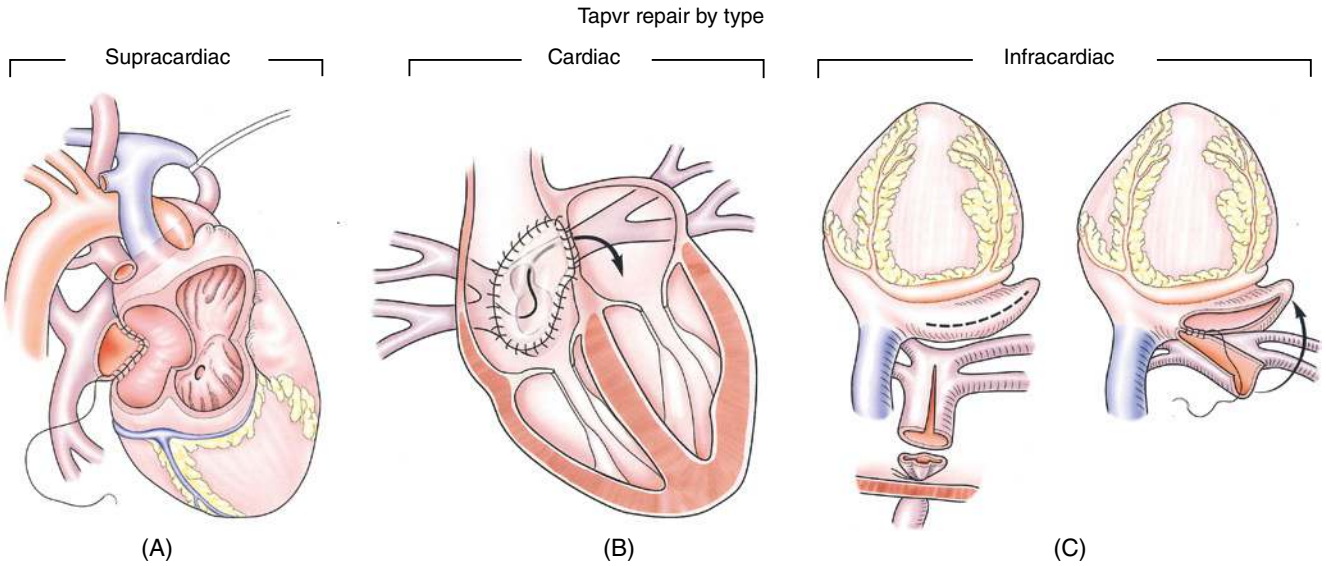


Figure 26.20 Examples of surgical techniques for the repair of total anomalous pulmonary venous return (TAPVR). (A) Supracardiac TAPVR: a transverse right atriotomy is extended across the atrial septum at the level of the atrial septal defect (ASD) and through the posterior aspect of the left atrium. The common pulmonary vein is anastomosed to the posterior wall of the left atrium and the supracardiac connection is ligated. The ASD and right atriotomy are then closed. (B) Cardiac TAPVR: The ASD is enlarged, with unroofing of the coronary sinus into the left atrium. An ASD patch is then used to channel pulmonary venous return to the left atrium. (C) Infracardiac TAPVR: With the heart rotated superiorly, the vertical vein is ligated at the level of the diaphragm. The common pulmonary vein and the posterior wall of the left atrium are incised and anastomosed. The ASD may be closed through an atriotomy. (Source: Gardner and Spray [168]. Reproduced with permission of Taylor & Francis.)

available in unobstructed TAPVR. Perioperative pulmonary hypertension occurs in as many as 50% of patients and is a major risk factor for early mortality [175, 176]. Pulmonary hypertensive crises may be avoided by employing hyperventilation, use of 100% oxygen, systemic alkalinization, sedation, paralysis, and inhaled nitric oxide. Sildenafil, magnesium sulfate, and prostaglandin E1 have been used in some patients to treat severe pulmonary hypertension [177]. Paradoxical pulmonary hypertension with systemic hypotension has been reported from the postoperative use of inhaled nitric oxide in patients with preoperative atrial obstruction and a poorly compliant and dysfunctional left ventricle. This paradoxical pulmonary hypertension is thought to be due to acute increases in pulmonary blood flow and resultant excessive preload to the noncompliant left side [178].

Pulmonary function may be compromised after bypass as a result of two pulmonary insults: (i) preoperative pulmonary edema secondary to pulmonary venous obstruction and (ii) the inflammatory response from cardiopulmonary bypass. Pulmonary compliance is decreased, and a large arterial-to-alveolar gradient develops. Pulmonary gas distribution may be optimized with the use of pressure control ventilation and altering PEEP to improve lung compliance.

Following repair, left atrial filling pressures may be elevated due to the small size and low compliance of the left atrium and ventricle. Accepting low blood pressures while weaning from CPB will help avoid overdistending the "unprepared" left side. Pulmonary artery pressures are frequently equal to or sometimes exceed, systemic pressures immediately after weaning from bypass. If the right ventricle is functioning adequately, this situation is often well tolerated for short periods as the PVR decreases in the first hour after bypass. Careful fluid management, optimization of heart rate and rhythm, and inotropic support will improve cardiac output. Temporary cardiac pacing may also be helpful. Perioperative dysrhythmias, especially supraventricular tachycardias, occur in as many as 20% of patients. If tolerated, an inovasodilator like milrinone will decrease left ventricular work and improve cardiac output. It is important to recognize that the Frank-Starling curve is very flat in the small, noncompliant LV, and administration of even small amounts of fluid may cause the left ventricle to become overdistended and fail.

KEY POINTS: PAPVR AND TAPVR

- PAPVR is often asymptomatic but may be associated with heart failure.
- PAPVR is managed similar to an ASD.
- TAPVR exists in four subtypes based on the anomalous connection: supracardiac, cardiac, infracardiac, and mixed.
- The pathophysiology of TAPVR is dependent on the presence and degree of pulmonary venous obstruction and the size of the interatrial communication.
- Obstructed TAPVR patients are particularly cyanotic and require 100% oxygen and significant ventilatory support pre bypass; inhaled nitric oxide (iNO) should be avoided.
- All TAPVR patients are at risk for post-bypass pulmonary hypertension, especially obstructed patients, and iNO should be available.
- TEE may cause or worsen the pulmonary venous obstruction.
- The chronically underfilled left ventricle may respond poorly to overloading after repair.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

5 Zuppa AF, Nicolson SC, Wilder NS, et al. Results of a phase I multicenter investigation of dexmedetomidine bolus and infusion in corrective infant cardiac surgery. Br J Anaesth 2019;123:839–52. Dexmedetomine shows promise with regard to neurologic outcomes following heart surgery in children. This study sought to establish the safety and pharmacokinetics of dexmedetomidine in neonates and infants undergoing heart surgery, including VSD repair. The authors found a low incidence of adverse events and validated a PK model of value in determining appropriate dosing.

22 Galexczka M, Szkutnik M, Bialkowski J, et al. Transcatheter patent ductus arteriosus closure: what have we learned after over 25 years? A single-center experience with 1036 patients. Kardiol Pol 2021;79:787–93. This report details the experience with a large cohort of patients undergoing transcatheter closure of PDA at a single institution. Outcomes are reported, and the observed major complication rate was 0.2%. Longitudinal follow-up showed superior results with duct occluders compared to other devices, with 100% complete closure after 1 year.

33 Backer CL, Mavroudis C. Surgical management of aortopulmonary window: a 40-year experience. Eur J Cardiothorac Surg 2002;21:773–9. The authors present their long-term experience in the surgical management of patients with APW. Repair techniques and outcomes are presented for 22 patients with various types of APW. A summary of experience at other institutions, including overall mortality among a total of 142 patients, is included.

45 Jensen B, Spicer DE, Sheppard MN, et al. Development of the atrial septum in relation to postnatal anatomy and interatrial communications. Heart 2017;103:456–62. This review article details the embryologic development of the atrial septum and seeks to dispel common misunderstandings about the septum secundum in particular. Included are details about the etiology of different ASD types and speculation about the reasons behind the differences in atrial septal development among vertebrates.

66 Laussen PC, Reid RW, Stene RA, et al. Tracheal extubation of children in the operating room after atrial septal defect repair as part of a clinical practice guideline. Anesth Analg 1996;82:988–93. This report on the safety and cost efficacy of surgical ASD repair compares three cohorts of patients from before and after the implementation of a clinical practice guideline on early extubation. Extubation in the operating room was associated with lower overall hospital charges but similar clinical outcomes. This early study has been corroborated in the more recent era (see Peterson et al. [62]).

76 Penny DJ, Vick GW. Ventricular septal defect. Lancet 2011;377:1103–12. The authors of this review article detail the anatomy, pathophysiology, diagnosis, and medical and surgical management of patients with VSDs.

110 Fudge JC, Li S, Jaggers J, et al. Congenital heart surgery outcomes in syndrome: analysis of a national clinical database. Pediatrics

2010;126:315–22. This study utilizes the Society of Thoracic Surgery Congenital Heart Surgery Database to retrospectively analyze a large cohort of patients with (n = 4,350) and without (n = 41,229) Down syndrome undergoing surgical repair of various heart defects, including AVC. There were no statistically significant differences in in-hospital mortality between groups. For AVC repair, there was a non-statistically significant trend toward decreased in-hospital mortality among Down syndrome patients compared with those without Down syndrome.

126 Kleinert S, Sano T, Weintraub RG, et al. Anatomic features and surgical strategies in double-outlet right ventricle. Circulation 1997;96:1233–19. This report provides a detailed summary of the anatomical features and subtypes of DORV. Long-term experience with surgical repair, including techniques and outcomes, is presented.

152 O'Byrne ML, Mercer-Rosa L, Zhao H, et al. Morbidity in children and adolescents after surgical correction of truncus arteriosus communis. Am Heart J 2013;166: 512–8. This study of truncus arteriosus patients in the child and adolescent age range found that morbidity, including hospitalization, cardiac reintervention, and non-cardiac operations, was highest in the first year of life. The authors also present evidence that comorbidities persist late after repair. These include truncal valve insufficiency and decreased indices of exercise tolerance (although mean right ventricular ejection fraction and end-diastolic volume were normal in this cohort).

173 Shi G, Zhu F, Wen C, et al. Single-institution outcomes of surgical repair of infracardiac total anomalous pulmonary venous connection. J Thor Cardiovasc Surg 2021;161:1408–17. This study considers the particularly at-risk subtype of infracardiac TAPVR, which is historically associated with high rates of post-repair pulmonary vein stenosis (PVS). The authors report their experience with 82 consecutive patients undergoing repair for this lesion. They found that the "sutureless" technique is associated with a lower risk of post-repair PVS compared to a conventional technique. Overall mortality was less than 10%, with a non-statistically significant trend toward lower mortality in the sutureless technique group.

CHAPTER 27
Anesthesia for Left–sided Obstructive Lesions

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Introduction

Left-sided obstructive lesions of the heart can occur at various anatomic levels and with varying degrees of severity, ranging from a bicuspid aortic valve with minimal hemodynamic compromise to aortic atresia and hypoplastic left heart syndrome (HLHS) with profound hemodynamic derangements. Imbalances in systemic blood flow may occur due to a circumscribed obstruction at a single level, such as in hypertrophic cardiomyopathy; coarctation of the aorta; interrupted aortic arch; and subvalvular, valvular, or supravalvular aortic stenosis, or from obstructions at multiple levels, such as seen in patients with Shone's complex. Depending on the specific type of left-sided obstruction, the child may also be at risk for pulmonary hypertension and/or impaired coronary perfusion during anesthetic care. A clear understanding of the level and degree of the obstruction is therefore important for optimal anesthetic management.

Aortic valve stenosis

Incidence, anatomy, and natural history

A normal aortic valve has three leaflets and occupies an area of around 2 cm^2/m^2 of body surface area. Although by some estimates, isolated congenital valvular aortic stenosis occurs in only approximately 2 per 10,000 births [1], it is associated with other cardiac lesions in more than 5% of children suffering from congenital heart disease (CHD) and presents with three to four times higher prevalence in males [2]. Valvular aortic stenosis may be associated with aortic coarctation and/or hypoplasia of the ascending and transverse arch, due to decreased antegrade blood flow in the fetus, which prevents adequate development of these structures. Aortic stenosis (AS) has been described as part of Hunter's, Hurler's, and Turner's syndromes. Structural variations from the customary tricuspid contour of the aortic valve are common and result in a bicuspid or monocuspid appearance

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of the valvular apparatus, whose formation starts during weeks 5–7 of embryonic development [3, 4]. The diseased valve leaflets are gelatinously or myxomatously malformed, and the commissures are often partially fused, leaving a diminished aortic orifice, which can be located eccentrically. Left ventricular myocardial hypertrophy is commonly observed, but non-hypertrophied left ventricular dilation has also been reported [5]. The age of diagnosis, clinical presentation, treatment modality, and timing of intervention depend not only on the degree of valvular obstruction but also on concomitant cardiac lesions and left ventricular size and function. Only a small minority (approximately 2%) of asymptomatic patients will develop aortic valve dysfunction by adolescence, and progression of the lesion is usually slow [6, 7]. Conversely, neonates with ductal-dependent critical AS may present in shock, requiring aggressive resuscitation and emergent intervention.

Pathophysiology

The diagnosis is typically made using transthoracic echocardiography (TTE), which provides comprehensive information regarding valve anatomy, annular size, aortic root diameter, and ventricular function (Table 27.1) [8, 9]. Continuous-wave mean Doppler gradients adequately predict the peak-to-peak transvalvular gradient as measured during cardiac catheterization, whereas peak instantaneous Doppler gradients slightly overestimate the transvalvular gradient [10, 11]. However, correcting the peak Doppler gradient for pressure recovery, a phenomenon describing the kinetic energy being transformed back to pressure energy as the velocity decreases distal to the stenosis, significantly improves agreement with subsequently measured catheter gradients [12]. Depressed left ventricular function, however, can lead to a misleadingly low gradient.

In the most severe form of critical AS, presenting in the neonatal period, systemic blood flow and coronary perfusion can often be dependent on retrograde blood flow via a patent ductus arteriosus (PDA). After spontaneous ductal closure, the affected neonates frequently present with symptoms of significant congestive heart failure, metabolic acidosis, and mitral valve insufficiency, quickly progressing to cardiogenic shock. Aggressive hemodynamic, respiratory, and metabolic resuscitation as well as immediate treatment with prostaglandin E_1 are essential to re-establish adequate systemic perfusion. In infants with a less dramatic presentation, left ventricular stroke volume is often maintained for extended periods of time. Normal ventricular wall tension is maintained by concentric ventricular hypertrophy; however, increased left ventricular systolic and end-diastolic pressures can result in impaired subendocardial perfusion and ischemia. In severe cases, this malperfusion leads to the replacement of the myocardium with a fibrous tissue, termed endocardial fibroelastosis, further impairing ventricular performance and diminishing survival [13–15].

Table 27.1 Grading of aortic stenosis severity

Severity	Mild	Moderate	Severe
Mean echo pressure gradient [mmHg]	<20	20–40	>40
Peak transvalvular velocity V_{max} [m/s]	2.0–2.9	3.0–3.9	>4.0
Indexed aortic valve area [cm^2/m^2]	>0.85	0.60–0.85	<0.6
Velocity ratio	>0.50	0.25–0.50	<0.25

Surgical and transcatheter approaches and outcomes

Treatment options and timing for intervention depend on the acuity of the clinical presentation and the concomitant cardiac abnormalities, as valvular aortic stenosis can cover a wide anatomical and pathophysiological spectrum. Patients with mild AS can be followed conservatively, and if aortic valve repairs or replacements are performed, outcomes are generally excellent [16], especially if achieved without patches [17]. Neonates suffering from critical AS, on the other hand, require immediate intervention. In this population, important consideration is given to the size and adequacy of the left ventricle to tolerate a one- or two-ventricle repair [18]. In order to predict a successful outcome with either biventricular or univentricular palliation (the latter is discussed in Chapter 30) in neonates with critical AS, several scoring systems have been developed (Table 27.2) [19]. Unfortunately, a recent single-center, retrospective study in 68 neonates did not find any of the binary score cutoffs to be predictive of successful biventricular *vs*. univentricular repair. In particular, the Rhodes and Discriminant scores

Table 27.2 Predictive scores for successful biventricular repair of critical aortic stenosis

Scoring System	Formula	Severe
Rhodes	14 (BSA + 0.943 (indexed aortic root) + 4.78 (long-axis ratio) + 0.157 (indexed mitral valve area) – 12.03	≥0.35
CHSS 1	30.55 (inverse of age at study entry [d]–1) – 6.20 (aortic root z-score) – 12.14 (echocardiographic grade of EFE) – 23.33 (logarithm of ascending aortic [mm]) – 28.30 (presence of moderate or severe tricuspid regurgitation) – 0.70 (LV long-axis length *z* score) – 86.47	<0
Discriminant	10.98 (body surface area) – 0.56 (aortic annulus z-score) – 5.89 (left ventricular to heart long-axis ratio) – 0.79 (grade 2 or 3 EFE) – 6.78	≥–0.65
CHSS 2	Multivariable regression equation using BSA, mitral valve *z* score, indexed heart long axis, minimum LVOT diameter, mid-aortic arch indexed	<0
2 V	[(Mitral valve annulus in 4Ch/aortic valve annulus in PSLA)/(Left ventricular length 4Ch/Right ventricular length 4Ch) + main pulmonary artery diameter]/BSA	≤16.2

BSA, body surface area; CHSS, Congenital Heart Surgeons' Society; LV, left ventricular; LVOT, left ventricular outflow tract; 4Ch, four-chamber; PSLA, parasternal long axis; BiV: biventricular; EFE: endocardial fibroelastosis; 2 V, two-ventricle.
(Source: Sachdeva et al. [19]. Reproduced with permission from Cambridge University Press.)

predicted the need for a univentricular approach in most patients who successfully maintained biventricular circulation after neonatal aortic valve intervention.

Given an adequate left ventricular size, the majority of pediatric cardiac centers currently favor percutaneous balloon valvuloplasty as the first treatment option for severe, ductal-dependent congenital AS. Using a retrograde approach, the balloon sheath is most commonly advanced from the femoral, umbilical, or carotid arteries. However, femoral vascular complications are not uncommon using this technique [20]. An alternative, antegrade approach can be used, in which the balloon is usually inserted from the femoral or umbilical veins, via the foramen ovale, into the left atrium and ventricle. If left ventricular function is adequate, administration of a bolus of adenosine (0.3–0.5 mg/kg), rapid right ventricular overdrive pacing (rate of 220–240/min), or an infusion of esmolol (200 μg/kg bolus followed by titrated infusion) during balloon dilation prevents forceful ventricular contraction against the balloon-occluded left ventricular outflow tract (LVOT) and ejection of the balloon from the aortic position with potential injury to the valve apparatus. In order to avoid post-interventional aortic valve insufficiency, the selected balloon size usually should not exceed the diameter of the aortic root. Using these techniques, severe aortic valve insufficiency can be avoided in greater than 80% of patients immediately after intervention, and the 5-year mortality typically remains below 20% [20–24]. If the left ventricle is of borderline size, significant aortic insufficiency would disqualify patients from single-ventricle palliation. See Chapter 34 for further discussion of percutaneous balloon aortic valvuloplasty.

Surgical options include primary surgical valvotomy, valvular repair, or replacement and depend on severity of the lesion and patient age. Advantages of an open approach include direct inspection and commissurotomy of the valve and the ability to address concomitant cardiac lesions such as PDA, ventricular septal defect (VSD), or aortic coarctation during the same procedure. However, the need for cardiopulmonary bypass (CPB) can increase morbidity for the patient. Historical case series using this approach have demonstrated an operative mortality of 0–18%, 5-year survival of 60–100%, aortic valve competency in greater than 95% of patients, and a 10-year freedom from reintervention of greater than 70% following surgical valvuloplasty [22, 25–28].

The Ross procedure, an aortic valve replacement with a pulmonary autograft combined with placement of a homograft in the pulmonary position, was introduced by Donald Ross in 1967 (Figure 27.1) [30]. The autograft can also be supported on the outside by a tube graft [31]. It can also be combined with enlargement of the LVOT, which is termed as the Ross–Konno procedure [29]. These procedures can be performed in neonates and infants, but have demonstrated better outcomes when performed in childhood or adolescence. Compared with prosthetic valve replacement, the Ross procedure uses autologous tissue and avoids the need for chronic anticoagulation. Long-term outcomes have been favorable, with greater than 75% freedom from reoperation up to 10 years postoperatively [32–35]. Allograft or prosthetic valve replacement is usually reserved for adolescent patients after completion of much of their somatic growth, if they are candidates for chronic anticoagulation.

More recently, reconstruction of the aortic valve with pericardial tissue has been described by Ozaki and colleagues [36] (Figure 27.2). The diseased aortic leaflets are excised and replaced with three pieces of glutaraldehyde-treated autologous pericardium trimmed to the size of the original leaflets, which are then attached to each annulus. Initial long and medium-term results in adults and children have been encouraging [37–39]. Table 27.3 presents the outcomes after aortic valve surgery in children.

During the past two decades, transcatheter aortic valve replacement (TAVR) has evolved from compassionate use in high-risk inoperable patients to an alternative modality to surgical valve replacement, even in lower risk patients [41]. A recent review in adult patients suggested a trend toward favoring a transcatheter over the surgical approach for aortic valve replacement, with a concomitant decline of in-hospital mortality for TAVR. TAVR has also been utilized in pediatric patients down to 4 years of age who were suboptimal surgical candidates; however, data on valve longevity is not yet available [42].

Experimental treatment options for critical AS or aortic atresia have included fetal transcatheter valvuloplasty [43]. The rationale for intervention, despite the risks for both mother and fetus, is to avoid single-ventricle palliation by preventing the natural progression of severe AS to HLHS. The treatment assumes that alleviating the restricted blood flow across the aortic valve will lead to improved growth and function of the left ventricle, thereby allowing a postnatal biventricular repair. However, fetal interventions for AS remain highly controversial and long-term outcomes are unclear [44, 45]. See Chapter 19 for further discussion of emerging treatment options.

Anesthetic considerations

Neonates with critical AS can present with significant metabolic derangement and hemodynamic instability. Anesthetic management is directed toward meeting the increased oxygen requirement of the hypertrophied left ventricular myocardium and optimizing cardiac output. Physiologic goals include maintenance of preload, afterload, and contractility. A normal or, to some extent, decreased heart rate is preferred. Bradycardia, however, is not well tolerated in neonates, whose cardiac output is heart rate-dependent given their fixed stroke volume, even without AS. Anesthetics that decrease systemic vascular resistance and/or increase heart rate must be used with caution to avoid myocardial ischemia and rapid deterioration of the patient's status. Vasoconstrictors such as phenylephrine can be used in this clinical scenario. Dysrhythmias are not uncommon during cardiac catheterization and should be treated aggressively.

Inotropic support with a medication such as epinephrine may be required if myocardial function becomes depressed, but must be used with caution given its ability to increase heart rate and myocardial oxygen requirement. In unstable patients, a high-dose opioid technique will facilitate both balloon valvuloplasty and surgical valvotomy. Occasionally, extracorporeal membrane oxygenation backup is arranged for selected high-risk patients.

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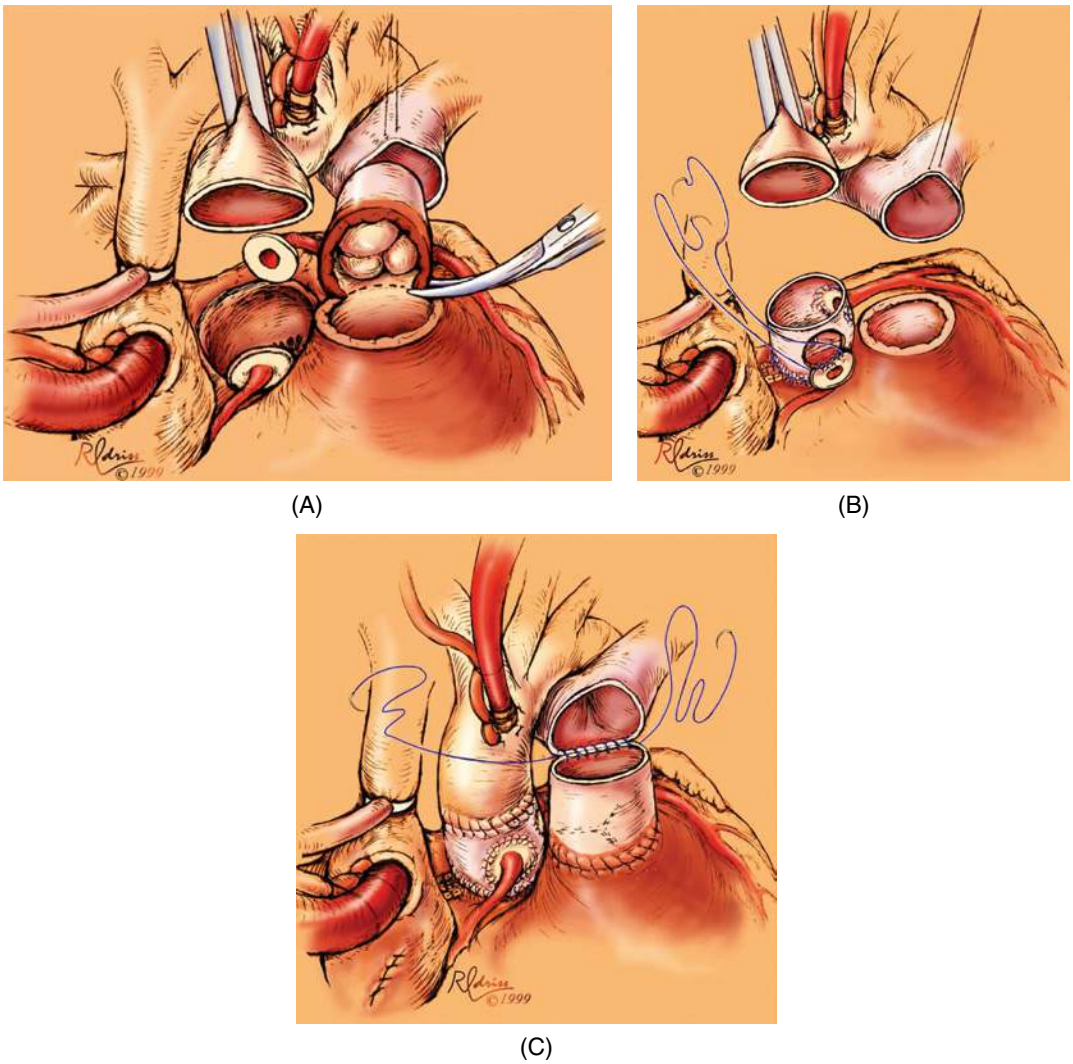


Figure 27.1 The Ross procedure (pulmonary autograft). (A) Incisions on the aorta, pulmonary artery, and the coronary buttons. (B) Pulmonary autograft and reimplantation of the coronary arteries. (C) Completing operation with pulmonary artery conduit to replace the native pulmonary valve. (Source: Mavroudis et al. [29]. Reproduced with permission from Cambridge University Press.)

KEY POINTS: VALVULAR AS

- Neonates may present in shock and require aggressive resuscitation prior to intervention.
- Transcatheter valvuloplasty is usually the treatment of choice in the neonate with severe or critical AS and adequate left ventricular size, with the major technical risk being overaggressive dilatation with resultant aortic valve insufficiency.
- Complications during balloon angiography include profound myocardial depression, bradycardia, asystole, and ventricular fibrillation.
- Anesthetic management with an opioid-based technique often facilitates maintenance of preload, afterload, contractility, and a low-normal heart rate; significant bradycardia should be avoided in the neonate.

Subvalvular AS

Incidence, anatomy, and natural history

Subvalvular AS (subAS) is a fixed obstruction occurring within the LVOT and accounts for approximately 1% of patients with CHD. Patients with subAS usually become symptomatic after infancy, with a higher male predilection of 2:1 to 3:1 [46]. Most commonly, the anatomic correlate of the LVOT obstruction is either a thin, discrete membrane of endocardial or fibrous tissue or a fibromuscular ridge emanating from the crest of the interventricular septum. Less common manifestations include a circumferential, fibromuscular ring that originates from the anterior mitral valve leaflet and a diffuse, tunnel-like fibromuscular obstruction. Other rare causes of subAS include anomalous attachments of mitral valve leaflets or mitral chordae. A variety of congenital heart lesions may exist in association with subAS and

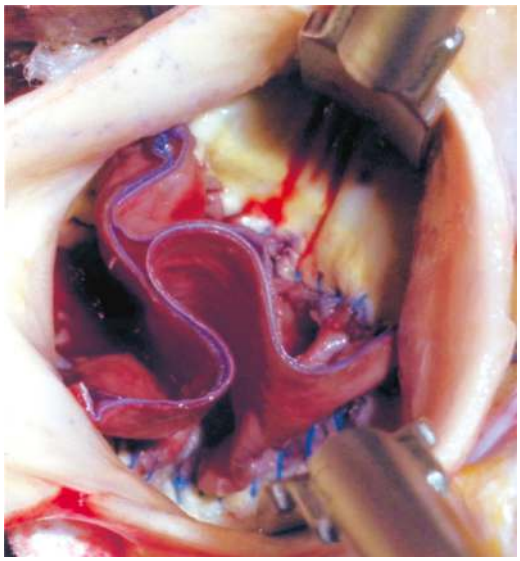


Figure 27.2 The Ozaki procedure. View of the coaptation of the three new aortic valve leaflets constructed using autologous pericardium. (Source: Ozaki et al. [36]. Reproduced with permission from Oxford University Press.)

Table 27.3 Outcomes after aortic valve surgery in children

	Neonates and infants	Older children
Aortic valve repair	Early mortality: 3–4% 10-year survival: 94% 10-year freedom from reoperation: 66%	Early mortality: 0.4–1.8% 10-year survival: 94% 10-year freedom from reoperation: 70%
Ross operation	Early mortality: 10–17% 10-year survival: 79% 10-year freedom from reoperation: 62%	Early mortality: 0–4% 10-year survival: 96% 10-year freedom from reoperation: 90%
Ozaki aortic valve replacement	Not yet reported	Early mortality: 0% 10-year survival: not reported 3-year freedom from reoperation: 80%
Mechanical aortic valve replacement	Not feasible	Early mortality: 0.5–7% 10-year survival: 82% 10-year freedom from reoperation: 78%
Homograft aortic valve replacement	Not reported	Early mortality: 5–13% 10-year survival: 85% 10-year freedom from valve reoperation: 50–60%

Source: Buratto et al. [40]. Reproduced with permission from Elsevier.

include bicuspid valves, AS, VSD, and aortic coarctation (Table 27.4). SubAS can occasionally present in infancy as part of Shone's complex or following the surgical closure of a VSD, but more commonly, the diagnosis is not made before the end of the first year of life and severity usually increases with age.

Table 27.4 Concurrent congenital anomalies in patients with subvalvular aortic stenosis

Lesions	Percentage of patients
Bicuspid valves	40
Aortic stenosis	28
Ventricular septal defect	24
Coarctation of aorta	12
Patent ductus arteriosus	12
Atrial septal defect	4

Pathophysiology

Patients usually present with complaints of orthopnea, dyspnea on exertion, or exertional angina and syncope. A systolic ejection murmur is present, most notable in the left, second, and third parasternal spaces, and a carotid artery thrill can be palpated in a significant number of patients. The diagnosis is confirmed by color Doppler echocardiography, which allows assessment of the degree of stenosis, biventricular enlargement and function, and concomitant mitral and aortic regurgitation. Cardiac catheterization is usually only needed to assess patients with serial obstructions or a tunnel-like stenosis. As the severity of subAS increases with age, progression of the LVOT obstruction may eventually lead to left ventricular diastolic dysfunction and pulmonary venous hypertension. Moreover, abnormal blood flow across the aortic valve can lead to thickening of the valve leaflets, causing valvular AS, left ventricular hypertrophy, damage to the aortic valve, and subsequent aortic insufficiency with progressive regurgitation. A higher LVOT gradient at diagnosis is an independent predictor for these adverse outcomes.

Surgical and transcatheter approaches and outcomes

Currently, surgery is favored as an early intervention for LVOT peak pressure gradients exceeding 40 mmHg and consists of fibromuscular resection with or without myectomy through an aortotomy (Figure 27.3), but timing remains controversial. A study comparing early and late surgery in 83 patients with subAS found that the LVOT gradient was successfully reduced in both groups, but that the late surgery group had a much higher recurrence rate at 5 and 10 years (28 and 57%, respectively) compared with the early surgery group (6 and 0%, respectively) [47]. Failure to intervene early also increases the risk of developing aortic regurgitation, which does not necessarily improve following subaortic resection. Transcutaneous balloon dilation is usually ineffective due to only temporary relief of the stenosis. Surgical complications include newly developed or worsened aortic insufficiency and postoperative atrioventricular heart block. In patients with tunnel-type subAS, an aortoventriculoplasty (Konno procedure) may be required or in the presence of aortic insufficiency, an aortic root replacement with a prosthetic valve or a Ross–Konno procedure is now favored. The Konno operation is still favored in patients with very small aortic annulus and involves an aortic incision above the aortic commissures and extended to the annulus and carried through the left and right ventricular outflow tracts, placement of a mechanical or bioprosthetic stented aortic valve, followed by

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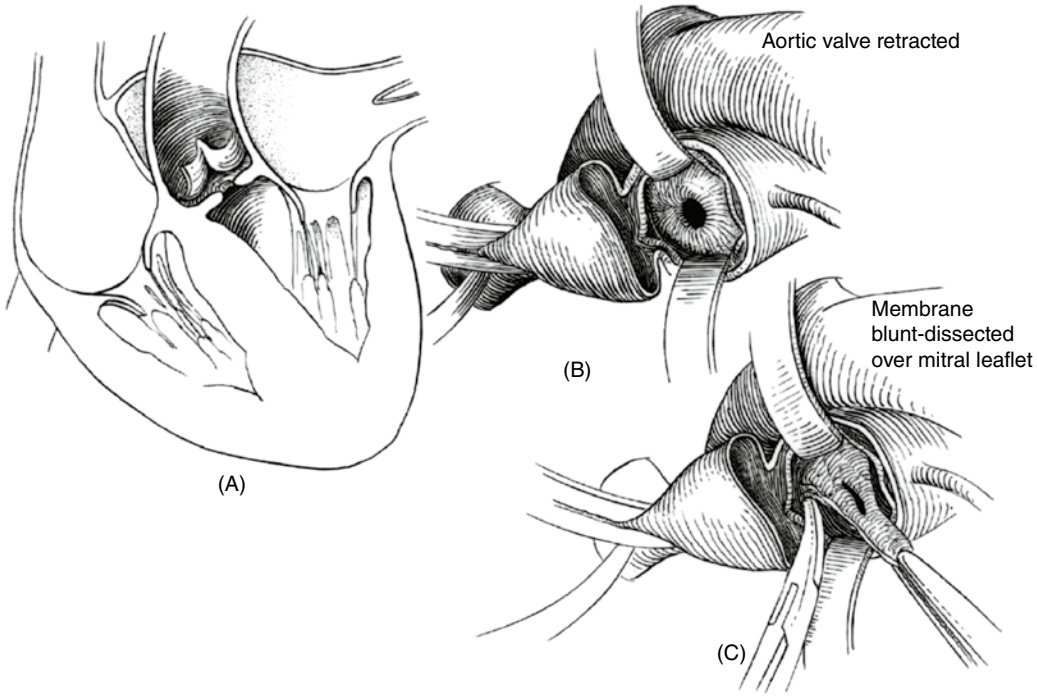


Figure 27.3 Surgical repair of subaortic stenosis. (Source: Adapted from Tworetzky et al. [43].)

closure with a pericardial or synthetic patch. Compared with the Konno operation, the Ross–Konno procedure requires less of an incision into the interventricular septum, limits right ventricular outflow tract distortion and potential injury to the conduction system (see also section on Shone's Complex later in this chapter). The operation involves harvesting the pulmonary valvular autograft, resection of the diseased aortic valve with coronary button mobilization, implantation of the pulmonary autograft and neoaortic reconstruction with coronary button anastomoses, followed by implantation of a pulmonary homograft into the right ventricular outflow tract. The use of an autograft provides growth potential and freedom from anticoagulation regimens [29].

Anesthetic considerations

Anesthetic management of subvalvular stenosis aims at maintaining the oxygen requirements of the myocardium and other end organs. Accordingly, the goal is to decrease myocardial oxygen demand and preserve both preload and afterload while maintaining or allowing a slightly decreased heart rate. In this regard, the anesthetic management of the patient with subAS is very similar to that for valvular AS.

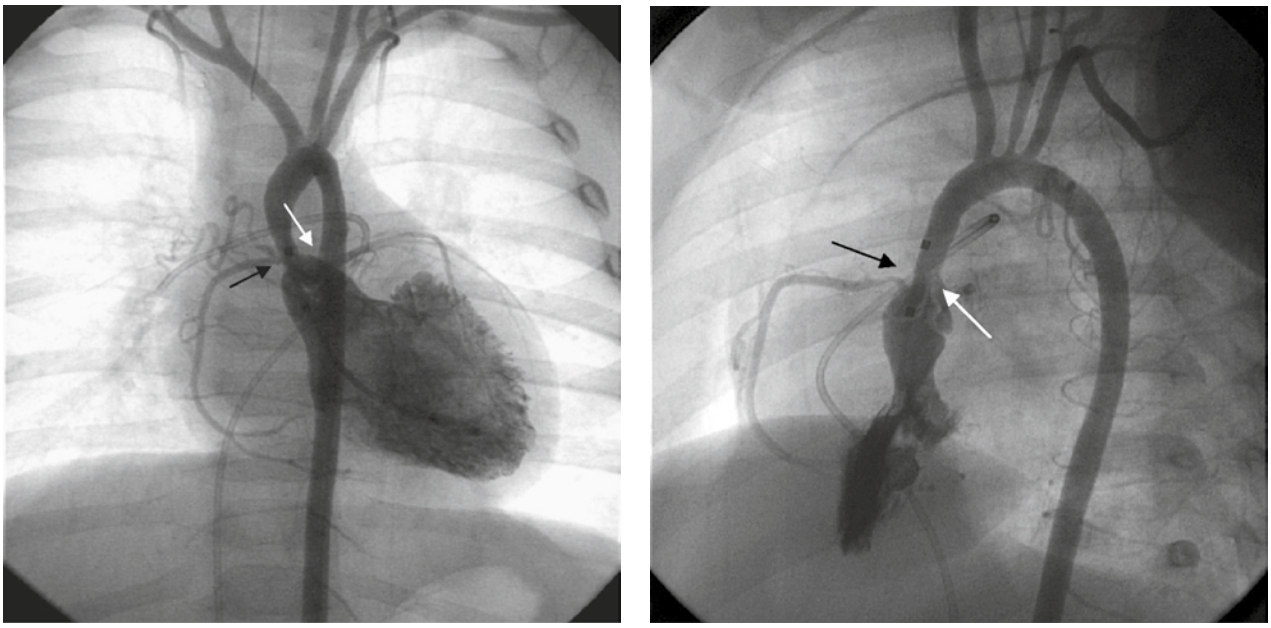
KEY POINTS: SUBVALVULAR AS

- Subvalvular AS usually consists of a discrete membrane in the LVOT presenting after infancy, but can also be seen as part of multi-level left-sided obstruction in patients with Shone's complex.
- Early surgical membrane resection with or without myectomy is favored over transcatheter approaches for an LVOT pressure gradient >40 mmHg.
- Hemodynamic goals during anesthetic management are similar to AS, maintaining preload and afterload, and allowing a slightly decreased heart rate.

Supravalvular AS

Incidence, anatomy, and natural history

Congenital supravalvular AS is the least common fixed obstruction of the LVOT, accounting for less than 0.05% of CHD. However, caused by abnormalities in the elastin gene (ELN), supravalvular AS occurs in up to two-thirds of patients with Williams–Beuren syndrome, also known as Williams syndrome, and as part of familial supravalvular AS [48–51]. The outflow tract obstruction frequently arises as a concentric narrowing of the ascending aorta at the superior margin of the sinuses of Valsalva, creating a typical hourglass deformity of the aorta [52]. Other manifestations include a diffuse narrowing along the entire ascending aorta or a fibrous semicircular membrane at the sinotubular junction. Supravalvular AS is a progressive disease, usually diagnosed after infancy, but may present earlier in life in patients with Williams syndrome. Coronary artery involvement, which is common in children with Williams syndrome, may include a reduction of the left coronary artery ostial size, ostial obstruction by fusion of the aortic cusp to the supravalvular ridge, or diffuse narrowing of the left coronary artery (Figure 27.4). In cases of mild supravalvular



(A) (B)

Figure 27.4 Representative angiogram of a patient with Williams syndrome, demonstrating supravalvular aortic stenosis (black arrow) and left coronary artery ostial stenosis (white arrow). (A) Anteroposterior view. (B) Lateral view. Peak systolic gradient during catheterization was 70 mmHg. (Source: Robert Beekman, MD. Reproduced with permission.)

AS, one case series found spontaneous improvement in the obstruction with time in 16% of patients and complete resolution in another 12% [53].

Pathophysiology

The underlying mechanism for supravalvular AS in Williams syndrome is an elastin arteriopathy, leading to a lack of elastic tissue in the walls of large arteries, increased amounts of collagen, and hypertrophy of smooth muscle cells [54]. Accordingly, pulmonary artery stenosis is also observed in over 30% of these patients, which can lead to biventricular hypertrophy [50]. Supravalvular AS may also be associated with a bicuspid aortic valve and aortic valvular stenosis in up to 50% of patients [55]. Concentric left ventricular hypertrophy can lead to myocardial ischemia, which is exacerbated by concomitant coronary artery stenosis. The risk of sudden death may only be slightly raised in patients with sporadic supravalvular AS, but is significantly increased in patients suffering from Williams syndrome, compared with the general population [56, 57]. A low-pitched, crescendo–decrescendo, systolic murmur is commonly heard at the base of the heart, radiating to the right carotid artery. The diagnosis of supravalvular AS is routinely made using two-dimensional echocardiography, and Doppler echocardiography can be utilized to determine the pressure gradient across the ascending aorta. Electrocardiograms usually show left ventricular hypertrophy with special attention given to potential ischemic ECG changes. Patients with Williams syndrome, occurring in approximately 1 in 20,000 live births, are easily recognized due to their characteristic facial dysmorphisms; common features include a wide mouth with full lips, micrognathia, dental malocclusion, widely spaced teeth, a short nose with a flat nasal bridge, and a long philtrum. They may also suffer from arterial hypertension, hypercalcemia with nephrolithiasis, esotropia, a hoarse voice, joint hyperelasticity, and sensorineural hearing loss. Although patients often exhibit cognitive impairment, they commonly have a characteristic desire for conversation and company with a lack of social inhibition [50, 58]. The suspected diagnosis of Williams syndrome can be verified even in neonates who do not yet exhibit the characteristic features, using genetic testing for karyotype and the fluorescent in situ hybridization (FISH) test for the 7q11.23 elastin gene deletion [54]. See Chapter 8 for futher discussion of Williams Syndrome.

Surgical and transcatheter approaches and outcomes

Infants with a peak pressure gradient of less than 20 mmHg across the supravalvular stenosis often remain stable and do not require intervention; however, a peak instantaneous pressure gradient of greater than 75 mmHg is usually an indication for surgical intervention [40]. Surgical techniques for repair of supravalvular stenosis include patch aortoplasty with one (Figure 27.5) or multiple patches [59, 60], complete excision of the stenotic ring with end-to-end anastomosis, or the Ross or Ross–Konno procedures [55, 61]. Significant coronary ostial obstruction may be relieved by a patch enlargement of the coronary os, excision of the obstructing aortic leaflet, or coronary artery bypass grafting [62]. Concomitant pulmonary artery stenosis in many patients with Williams syndrome is frequently addressed by balloon dilation of the right ventricular outflow tract stenosis prior to surgical repair of the LVOT obstruction.

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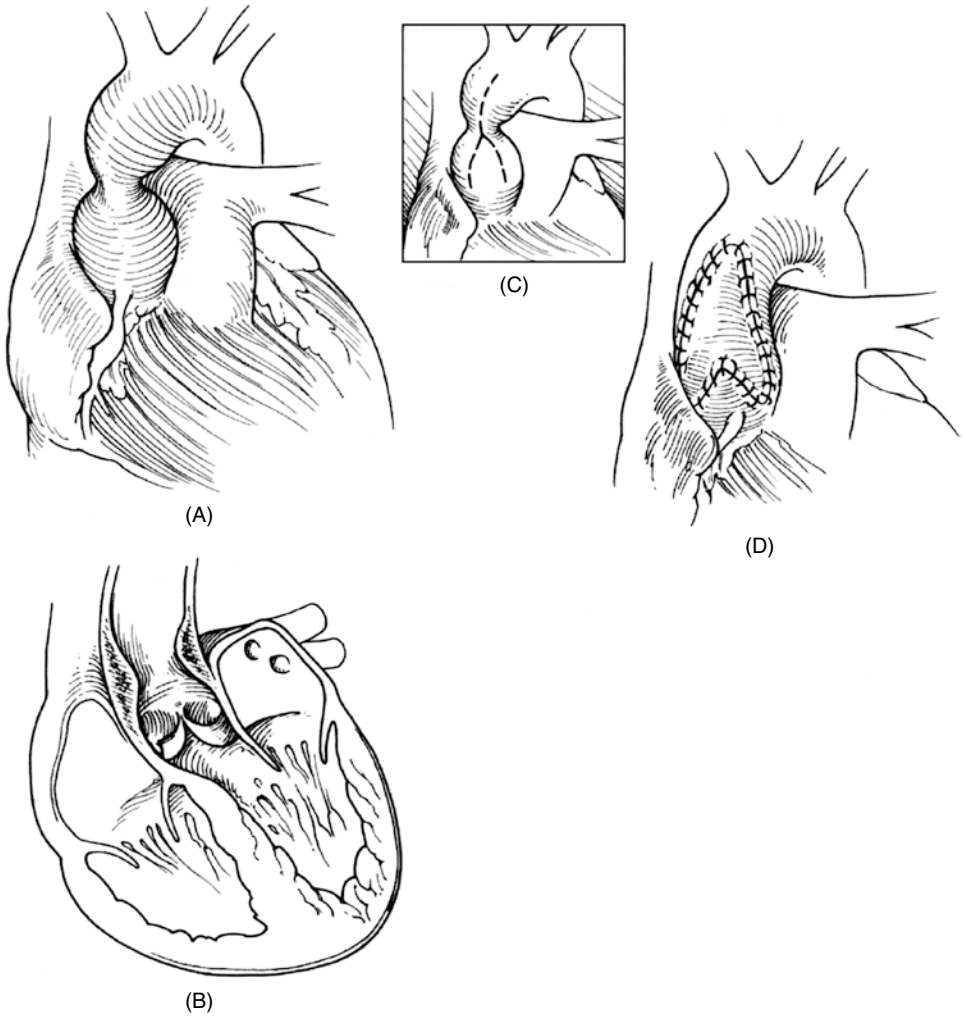


Figure 27.5 Repair of supravalvular aortic stenosis. (A) External appearance. (B) Coronal plane view of the defect. (C) Inverted Y incision in the ascending aorta. (D) Placement of an autologous pericardial patch. (Source: Chang et al. [59]. Reproduced with permission from Wolters Kluwer Health, Inc.)

Anesthetic considerations

Supravalvular AS shares many of the pathophysiological characteristics and anesthetic management requirements of valvular and subvalvular stenosis. However, due to the potential combination of supravalvular AS, left ventricular hypertrophy, right ventricular outflow tract obstruction, and coronary artery disease, patients with Williams syndrome can be at significantly increased risk for anesthesia-related complications. Accordingly, several reports have described perioperative fatalities in these patients, ranging from events during anesthesia induction or intubation to postoperative complications [56, 63–67]. The majority of these reported events seemed to be caused by myocardial ischemia. Maintaining afterload at slightly elevated levels is therefore paramount to preserve coronary perfusion pressure. Volatile anesthetics must be used with caution due to their myocardial depressive and vasodilatory effects. Intramuscular premedication with ketamine may facilitate the establishment of intravenous access, and high-dose opioid techniques may accomplish the anesthetic goals. However, significant increases in heart rate, which can occur following administration of ketamine or vagolytic agents, are not well tolerated and need to be treated aggressively. Also, arrhythmias, such as those caused by catheter manipulation during cardiac catheterizations, are frequently poorly tolerated. It must be emphasized that the coronary arteries are frequently significantly involved, being partially obstructed or "hooded" from the abnormal surrounding connective tissue in the aorta, and the degree of coronary obstruction often does not correlate with the severity of the supravalvular AS. Other anesthetic complications, such as difficult mask ventilation or difficult tracheal intubation, may arise due to the concomitant facial deformities in this syndrome. Moreover, the potential development of abnormal skeletal muscle tissue with lipid deposits may lead to an increased sensitivity to muscle relaxants, thus warranting close monitoring of neuromuscular blockade [68]. Additional sources of perioperative morbidity include their predisposition to renal insufficiency and arterial hypertension, which need to be appropriately addressed in the anesthetic plan. Preoperative risk assessment is difficult, because adequacy of coronary blood flow is difficult to verify and the more reliably quantifiable degree of supraaortic stenosis does not necessarily correlate with the degree of coronary abnormalities. In particularly, for critical patients,

extracorporeal membrane oxygenation (ECMO) or CPB backup may be advised as cardiopulmonary rescuscitation can be challenging in these patients.

KEY POINTS: SUPRAVALVULAR AS

- Supravalvular AS occurs in two-thirds of patients with Williams syndrome and can be accompanied by coronary and ostial stenoses, substantially increasing the risk of coronary events and sudden death.
- Maintain preload and afterload at high-normal levels to preserve coronary perfusion pressure, and maintain heart rate and contractility at low-normal levels.
- Avoid anesthetic techniques that produce significant decreases in preload and afterload, e.g., high doses of volatile anesthetics and/or propofol.
- Tachycardia is not well tolerated in patients with significant coronary stenosis and must be treated aggressively.

Hypertrophic cardiomyopathy

Incidence, anatomy, and natural history

Hypertrophic cardiomyopathy (HCM) is a cardiac disorder with significant heterogeneity of etiology, anatomic findings, and clinical presentation; in adults, it occurs with an estimated prevalence of 1:500 [69, 70]. This disease is diagnosed less commonly in children, but when identified, it carries a significant risk for adverse outcomes, with an overall survival of 97% at 5 years and 94% at 10 years [71]. Over the past decade, the increased availability of genetic and metabolic testing has improved the ability to identify the underlying etiology of HCM. While in both adults and children, the most common cause of HCM is a mutation in sarcomeric genes, in the pediatric population, the etiology is more heterogeneous and non-sarcomeric causes represent up to 35% of cases of HCM [72] (Table 27.5).

In one single-center pediatric study, an affected family member, positive HCM gene panel mutation, metabolic disease, or genetic syndrome were identified in over 80% of patients with HCM. [61] Children presenting with HCM at less than 1 year of age carry a worse prognosis, and an inherited error of metabolism or malformation syndrome (e.g., RASopathies) is likely present [72, 73]. Genetics evaluation and testing is now recommended in all children diagnosed with HCM [71].

The characteristic gross morphologic feature in HCM is a hypertrophied and non-dilated left ventricle, and the absence of other disease processes capable of causing this degree of hypertrophy (e.g., AS). There is significant heterogeneity with regard to the location and degree of cardiac hypertrophy, and in fact, even first-degree relatives with familial HCM often exhibit different patterns of hypertrophy [74, 75]. Myocardial hypertrophy may occur in the anterior, posterior, and/or basal regions of the ventricular septum, and in the ventricular free wall. The hemodynamic severity is dependent on the particular region where hypertrophy is most prominent: significant hypertrophy of the anterior region of the ventricular septum compared with the posterior septum more commonly causes subaortic outflow obstruction [76]. Echocardiography is extremely helpful in determining the extent, location, and severity of the disease. Quantitative echocardiographic findings in patients with HCM include increased left ventricular wall thickness, decreased left ventricular end-diastolic cavity size, and increased left ventricular fractional shortening [77]. Other important findings include the presence and severity of LVOT obstruction, systolic anterior motion of the mitral valve, and mitral regurgitation [78]. Cardiac Magnetic Resonance Imaging (CMR) is also commonly used for diagnosis, risk prediction, and presurgical planning. This imaging modality provides extremely accurate information regarding LV wall thickness, ventricular chamber sizes, and the degree of myocardial fibrosis which has been shown to be a marker for increased risk for ventricular tachyarrhythmias and heart failure progression [79].

The natural history of this disease is dependent on multiple factors, including the underlying etiology, age at presentation, clinical signs and symptoms, and the presence of other co-morbidities. Most patients with HCM, and neonates in particular, often remain asymptomatic for a long period of time. Many patients are not diagnosed until they present with symptoms of congestive heart failure, cardiac rhythm disturbances, or syncope or following a near-death cardiac event [70]. HCM has become the leading cause of sudden cardiac death in young athletes [74, 75]. Even when the diagnosis is

Table 27.5 Non-sarcomeric causes of hypertrophic cardiomyopathy in children

Sarcomeric	
Malformation syndromes: RASopathies	Noonan syndrome
	Noonan syndrome with multiple lentigines
	Costello syndrome
	Cardiofaciocutaneous syndrome
Glycogen storage diseases	Pompe disease (glycogen storage disease type IIa)
	Danon disease (glycogen storage disease type IIb)
	Cori–Forbes disease (glycogen storage disease type III)
	PRKAG2 syndrome
Lysosomal storage diseases	Mucopolysaccharidoses
Mitochondrial disorders	
Fatty acid oxidation disorders	Very long-chain acyl-CoA dehydrogenase deficiency
	Multiple-acyl-CoA dehydrogenase
	Long-chain hydroxyacyl-CoA dehydrogenase
	Carnitine-acylcarnitine translocase
	Carnitine palmitoyltransferase II
	Carnitine-acylcarnitine translocase deficiency
Endocrine disorders	Primary hyperinsulinism
	Infant of a mother with diabetes mellitus
	Acromegaly

Source: Monda et al. [72] / Frontiers Media S.A. / CC BY 4.0.

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made prior to a catastrophic event, the clinical course of the disease is inconsistent and dependent on whether the HCM is obstructive or non-obstructive. If obstructive, more than 25% of infants will develop symptoms of congestive heart failure manifested by feeding intolerance or failure to thrive [80].

Pathophysiology

Hypertrophic cardiomyopathy is most commonly caused by mutations in genes encoding proteins of the myocardial sarcomere, and in fact over 50 mutations causing the disease have been identified, making it one of the most widespread genetic diseases of the myocardium. Depending on the specific mutation, abnormalities in the protein may lead to ineffective contraction of the sarcomere and the development of myocyte hypertrophy [70]. The histology of the left ventricle is remarkable for disarray of the hypertrophied cardiac muscle cells, myocardial scarring and fibrosis, and thickened walls in small intramural coronary arteries causing luminal narrowing [76, 81]. Although fiber disarray is present even in normal hearts, the extent to which this happens in the heart with HCM is significantly increased [82]. A minority of patients may progress to a secondary phase characterized by wall thinning in areas of previous hypertrophy, enlargement of cavity size, and impairment of ventricular function, a phenomenon likely related to myocardial ischemia and necrosis [76].

Hypertrophic cardiomyopathy also presents in infancy without sarcomeric protein gene mutations, such as in infants of insulin-dependent diabetic mothers, children with malformation syndromes such as Noonan syndrome, or in patients with glycogen storage diseases such as Pompe disease. In Noonan syndrome, a genetic disorder commonly associated with congenital cardiac disease, approximately 15–20% of children have HCM, with less favorable outcomes than children with non-syndromic HCM [80, 83]. Pompe disease represents a glycogen storage disease type II (GSD-II) which is a rare autosomal recessive disorder occurring in 1 out of 40,000 live births, in which lysosomal glycogen accumulates in both cardiac and skeletal muscle due to a deficiency of acid α-glucosidase [84, 85]. Children presenting with the infantile form of this disease exhibit severe HCM, and, if untreated, often die in the first year of life from respiratory or cardiac complications. Therapy with long-term intravenous recombinant α-glucosidase often leads to significant resolution of the cardiac hypertrophy and skeletal muscle weakness [86] Infants presenting for surgery prior to therapy with recombinant human α-glucosidase are at a high risk for anesthetic complications [87]. In a retrospective review, 6% of patients with infantile-onset Pompe disease receiving anesthetics developed an arrhythmia or cardiac arrest soon after induction of anesthesia [88]. Two-thirds of these events were attributed to the use of sevoflurane or propofol.

The most common finding in patients with HCM is a hyperdynamic left ventricle with abnormal diastolic relaxation and compliance; LVOT obstruction is present in no more than 25% of patients [89] (Figure 27.6). The degree of outflow tract obstruction is a dynamic process and may be reduced or abolished by decreasing myocardial contractility, increasing preload, or increasing afterload. Conversely, the dynamic obstruction is increased during periods of increased ventricular contractility or sympathetic stimulation, as for instance, with exercise. The outflow tract gradient is felt to be caused in part by anterior movement of the mitral valve toward the ventricular septum during early systole, and more likely to occur in the setting of a hypertrophied anterior septum [89]. Anterior movement of the mitral valve may interfere with optimal valve closure, causing mitral regurgitation, occurring more commonly in the setting of LVOT obstruction. The combination of severe left ventricular hypertrophy, LVOT obstruction, and abnormalities of the intramural coronary arteries all place these patients at an increased risk of myocardial ischemia and ventricular arrhythmias.

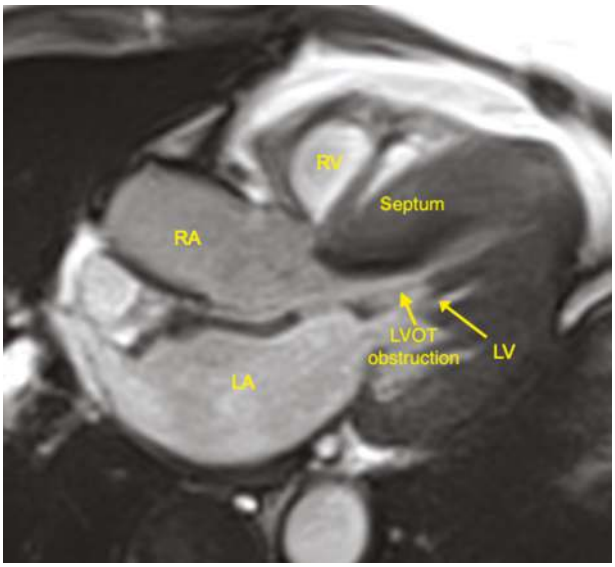


Figure 27.6 MRI image of a patient with severe hypertrophic cardiomyopathy causing left ventricular outflow tract (LVOY) obstruction. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. (Source: Courtesy of Michael Taylor, MD.)

Surgical and transcatheter approaches and outcomes

Treatment modalities for HCM include medical therapy, surgical therapy, the use of pacing and/or implantable cardioverter-defibrillators, and cardiac transplantation. Aggressiveness of therapy in any given patient depends on the risk factors for morbidity and mortality. Identified risk factors for patients with HCM include family history of sudden death or syncope, extreme septal hypertrophy, and LVOT obstruction [90, 91]. Asymptomatic patients with HCM may not require any therapy. When medical therapy is initiated, it usually consists of either a β-blocker or calcium-channel blocker, and can be guided by treadmill exercise testing or patient symptoms [70]. Another treatment option is dual-chamber pacing, which has been used as an alternative to surgery with mixed results. Although pacing has been shown to be of benefit in some patients, randomized controlled trials showing long-term improvement in outcomes are lacking. For patients with HCM that have had a sudden cardiac death event and/or sustained ventricular tachycardia/ventricular fibrillation, placement of an implantable cardioverter-defibrillator is indicated [79].

Indications for surgical intervention include a left ventricular outflow gradient >60 mmHg, significant symptoms such as dyspnea, angina, or syncope unresponsive to medical therapy, and an increase in mitral regurgitation [92]. Septal myectomy is an effective treatment in both pediatric and adult patients [76, 78]. In pediatric patients with HCM undergoing septal myectomy at the Mayo Clinic over a 28-year period, there were no early deaths and survival rates at 5 and 10 years were 97 and 95%, respectively. Late follow-up was remarkable for 96% of patients remaining in New York Heart Association (NYHA) functional class I or II [91]. The surgical approach is commonly transaortic, and often technically challenging in smaller children. Transesophageal echocardiography (TEE) can be used to aid in the assessment of intracardiac anatomy before resection and of the adequacy of resection following myectomy. Despite an excellent surgical result with minimal residual left ventricular outflow gradient, these children remain at risk for cardiac arrhythmias and sudden death [91]. Patients with congestive heart failure, myocardial ischemia, and/or life-threatening arrhythmias, despite optimal medical and surgical therapies, may be considered for cardiac transplantation.

Anesthetic considerations

Patients with HCM are at a significant risk for cardiac complications during anesthesia and surgery. A recent retrospective study looking at the incidence of complications in children with HCM undergoing general anesthesia at a tertiary care pediatric center demonstrated a 0.6% mortality rate; minor complications were seen in 12% of patients [92]. One adult study was remarkable for 40% of patients experiencing at least one perioperative adverse cardiac event, and predictors of adverse outcome included major surgery and duration of surgery [93]. To avoid hemodynamic instability, anesthetic management should be tailored toward maintaining preload and afterload, decreasing myocardial contractility, and avoiding tachycardia. Maintenance of normovolemia prior to induction is vital, and the placement of an intravenous catheter and administration of intravenous fluids prior to surgery may be beneficial. While halothane meets many of the hemodynamic goals and has been well tolerated in such cases, it is no longer available [94]. Sevoflurane and desflurane, on the other hand, may cause significant increase in heart rate and reduction in systemic vascular resistance and should be used with caution. The use of an intravenous access for anesthetic induction allows for careful titration of anesthetic agents and for rapid treatment of hypotension and/or cardiac arrhythmias. High-dose opioid anesthesia provides stable hemodynamics and maintenance of a normal to low heart rate. Remifentanil, a short-acting potent opioid administered by continuous infusion, may be an excellent choice when extubation of the trachea following surgery is planned. For patients not already on β-blocker therapy, esmolol can be used in the perioperative period to control heart rate and reduce cardiac contractility.

Depending on the procedure and severity of HCM, arterial vascular access and central venous access may be indicated. Patients with a critical LVOT gradient may benefit from pre-induction placement of an arterial line for close monitoring of systemic blood pressure during anesthetic induction. However, one must carefully judge whether the increased anxiety and pain caused by the procedure might precipitate an adverse event. During placement of a central venous line the patient must be closely monitored for the occurrence of an atrial dysrhythmia. Rapid treatment of dysrhythmias is important, as hemodynamics may deteriorate swiftly. Central venous pressure may be significantly elevated in patients with HCM due to the hypertrophied noncompliant ventricle.

KEY POINTS: HYPERTROPHIC CARDIOMYOPATHY

- Hypertrophic cardiomyopathy is a heterogeneous condition caused by multiple factors including mutations in genes encoding sarcomeric proteins, metabolic and mitochondrial disorders, and RASopathies such as Noonan and Costello syndrome.
- Characteristic anatomic features include a hypertrophied left ventricle with hyperdynamic systolic function and abnormal diastolic relaxation.
- Hypertrophic cardiomyopathy currently is the leading cause of sudden death in young athletes.
- Anesthetic considerations include maintaining preload at high-normal levels, decreasing myocardial contractility, and avoiding tachycardia.

Coarctation of the aorta

Incidence, anatomy, and natural history

Coarctation of the aorta denotes a narrowing of the aortic lumen and is most often located just distal to the opening of the left subclavian artery at the point of insertion of the ductus arteriosus (Figure 27.7). Although usually presenting as a discrete narrowing, the coarctation can also be a long-segment stenosis or be associated with hypoplasia of the transverse aortic arch. Up to 8% of patients with CHD have an aortic coarctation, which is more prevalent in males than females by a 1.5:1 ratio [2, 94]. The etiology of the coarctation is a folding of the medial tissue of the aortic wall; the obstructing shelf is often composed of circumferential ductal tissue, and with ductal closure contraction of this tissue leads to aortic coarctation. Both proximal and distal transverse arch hypoplasia is common and defined as less than 60% or 50% respectively of the diameter of the ascending aorta [95]. When the coarctation is severe with limited anterograde flow from the transverse arch, blood flow to the distal aorta may be entirely dependent on a PDA. If the coarctation segment remains uncorrected for a prolonged period of time, collateral blood flow will develop, thus allowing for adequate perfusion distal to the aortic obstruction. Other congenital cardiac anomalies are present in about one-half of patients with aortic coarctation and include ventricular septal and atrioventricular canal defects, valvular AS, and subvalvular AS.

If untreated, the natural history of aortic coarctation is primarily related to the severity of the obstruction. Over 90% of untreated patients with coarctation of the aorta die by the

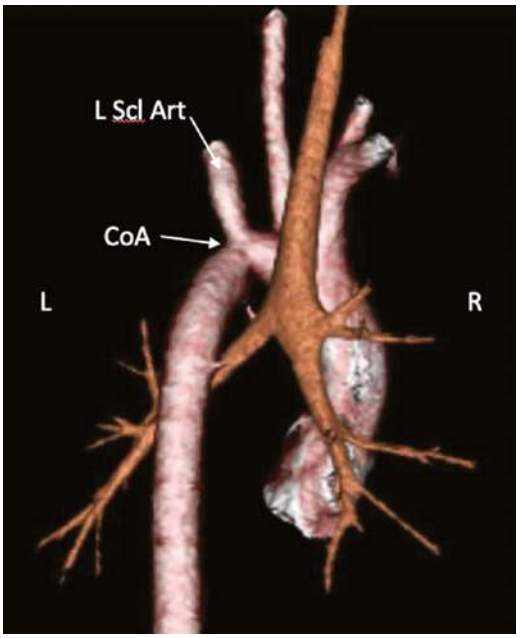


Figure 27.7 Posterior-anterior computed tomography imaging of an infant with an aortic coarctation located just distal to the left subclavian artery. L, patient's left side; R, patient's right side; CoA, coarctation; L Scl Art, left subclavian artery. (Source: Courtesy of Michael Taylor, MD.)

age of 50 [96]. Even with surgical repair, patients with aortic coarctation demonstrate an increased predilection for hypertension, coronary artery disease, stroke, heart failure, and ruptured aortic and cerebral aneurysms. Over 50% of patients have arterial hypertension at long-term follow-up, which is not necessarily related to the presence of a recurrent stenosis [97]. Patients who have undergone aortic coarctation repair during infancy without residual stenosis also exhibit abnormal left ventricular diastolic function and aortic elasticity as adults [98].

Pathophysiology

The neonate with a severe coarctation generally presents during the first few weeks of life with congestive heart failure, left ventricular systolic dysfunction, and, in some cases, cardiogenic shock. The closure of the ductus arteriosus causes an acute increase in left ventricular afterload, elevation of left ventricular end-diastolic pressure, reduction in stroke volume, pulmonary venous congestion, and pulmonary artery hypertension [2]. The infant with a less severe coarctation may exhibit tachypnea and failure to thrive. Still, the asymptomatic child with an unrecognized coarctation is at an increased risk for developing systemic hypertension proximal to the coarctation and subsequent left ventricular failure.

The diagnostic feature of aortic coarctation is a systolic blood pressure difference between the upper and lower extremities. TTE [99] using a suprasternal long-axis view typically shows a localized narrowing ("posterior shelf") just distal to the left subclavian artery, and Doppler analysis aids in assessing the severity of the coarctation. Evaluating the heart for other associated lesions is important. Magnetic resonance imaging (MRI) and computed tomography (CT) angiography with three-dimensional reconstruction are other modalities used to image the aortic arch, and are more commonly utilized in older children and adults where imaging by TTE is often suboptimal. A study comparing CT angiography with TTE for diagnosis of coarctation demonstrated that CT angiography was the more sensitive test (100% vs. 87.5%) [100]. Drawbacks to these modalities include the use of ionizing radiation with CT angiography and the necessity for anesthesia or sedation for MRI in younger children.

Surgical and transcatheter approaches and outcomes

Therapeutic options for aortic coarctation include surgery, balloon dilation, and placement of endovascular stents. However, there continues to be significant debate regarding the optimal long-term treatment strategy. At the present time, neonates and infants are thought to have a superior outcome with surgical repair, while older patients may benefit from balloon dilatation with or without stenting as the initial therapy [101]. A retrospective study comparing balloon angioplasty and surgery as the initial therapy for neonatal coarctation showed that over 80% of patients undergoing balloon angioplasty subsequently required surgery or repeat balloon dilation, while less than 20% of patients undergoing surgery required reintervention [102]. Another study comparing outcomes in children undergoing balloon angioplasty for native coarctation found that the incidence of restenosis and aneurysm formation was significantly increased in children <1 year of age [101]. The options for surgical repair include a subclavian flap aortoplasty, a resection of the narrowed portion of the aorta with a traditional end-to-end anastomosis, extended end-to-end or end-to-side reconstruction (aortic arch advancement technique), or an interposition tube graft (Figure 27.8). The aortic arch advancement technique is used when significant transverse arch hypoplasia is present and requires proximal extension of the anastomosis onto the underside of the transverse arch up to the level of the innominate artery [103] This operation can be performed through a left thoracotomy approach or median sternotomy with cardiopulmonary bypass (CPB). Indications for a median sternotomy and CPB include significant transverse hypoplasia and the need for repair of a concomitant cardiac lesion such as a ventricular septal defect. Repair through a left thoracotomy requires placement of a cross-clamp just distal to the innominate artery, placing the patient at risk for cerebral hypoperfusion. Some controversy exists regarding the degree of transverse arch hypoplasia necessitating a median sternotomy approach. A recent single-center retrospective study concluded that median sternotomy should be considered for patients with distal transverse arch z-scores lower than −2.8 and proximal transverse arch z-scores lower than -4.1, and that with the left thoracotomy approach there was a low mortality rate, reintervention rate, and incidence of hypertension [104]. Other perioperative complications from surgical repair of coarctation include recurrent laryngeal nerve or phrenic nerve injury, chylothorax, bleeding, and rarely paraplegia (0.4%) [105].

Restenosis after surgical repair of aortic coarctation is not uncommon, with an incidence that varies widely depending

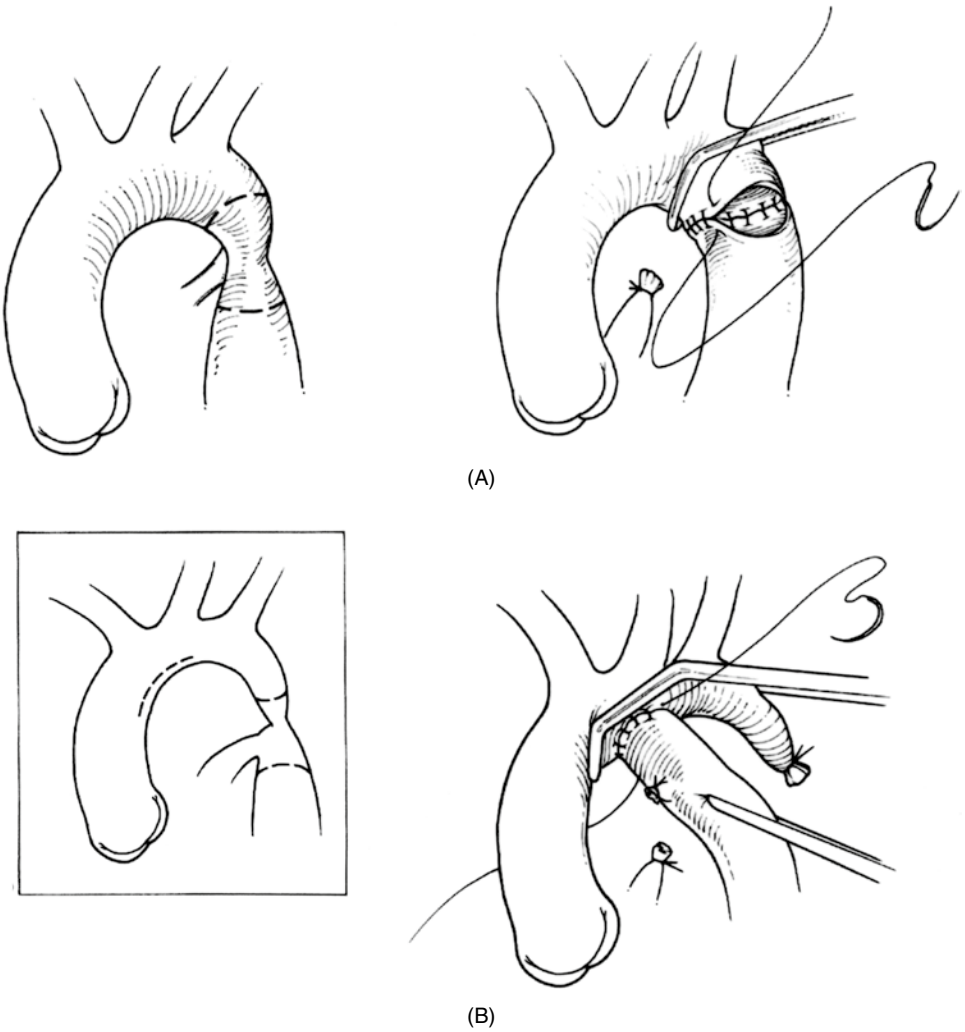


Figure 27.8 Two surgical approaches for repair of coarctation of the aorta. (A) Resection of coarctation with end-to-end anastomosis. (B) End-to-side, or aortic arch advancement technique. (Source: Chang et al. [59]. Reproduced with permission from Wolters Kluwer Health, Inc.)

on the surgical technique, age of patient at time of repair, definition of recurrence, and length of follow-up [106]. A study examining long-term complications in a cohort of patients up to 27 years after repair found a restenosis rate of 11%, with restenosis defined as a systolic brachial–ankle blood pressure difference of greater than 20 mmHg [97]. Earlier studies showed a higher incidence of recoarctation if the operation was performed in the first 3 years of life; the recurrence rate was <3% if performed afterward [107]. A more recent study utilizing MRI in adults that had undergone aortic coarctation repair during childhood found recoarctation and local aneurysm formation in 48 and 21% of patients, respectively [108]. Current surgical techniques emphasizing aggressive excision of ductal tissue and the use of an extended end-to-end anastomosis in the setting of arch hypoplasia may lead to a lower incidence of restenosis. Because of the significant prevalence of hypertension and other long-term sequelae following coarcation repair, many centers aggressively treat even mild recurrent stenosis in the interventional catheterization suite.

The use of balloon angioplasty for initial treatment of discrete aortic coarctation in children frequently provides excellent immediate hemodynamic results [99, 101, 109]. Reluctance to use this approach in some centers is related to concerns about restenosis and aneurysm formation, which occur in 10–20% and 5–10% of patients, respectively [100]. Approximately 25% of children undergoing an initial balloon angioplasty will require a reintervention within 2 years [99, 101]. Balloon angioplasty is generally accepted as the first-line therapy for restenosis following surgical repair of aortic coarctation, providing excellent immediate and long-term results [106, 110, 111]. In approximately 80% of cases, the residual systolic pressure gradient can be reduced to less than 20 mmHg. Repeat balloon angioplasty or surgery is required in about 25% of these patients due to restenosis [106]. Complications related to balloon angioplasty include femoral artery thrombosis, aortic rupture, and stroke. The risk of femoral artery injury is greater in the smaller child. An increased mortality risk has been reported for patients undergoing angioplasty for recurrent coarcation versus native coarctation [110].

Balloon-expandable endovascular stents provide an effective therapy for the treatment of native or recurrent coarctations occurring after surgery or balloon angioplasty

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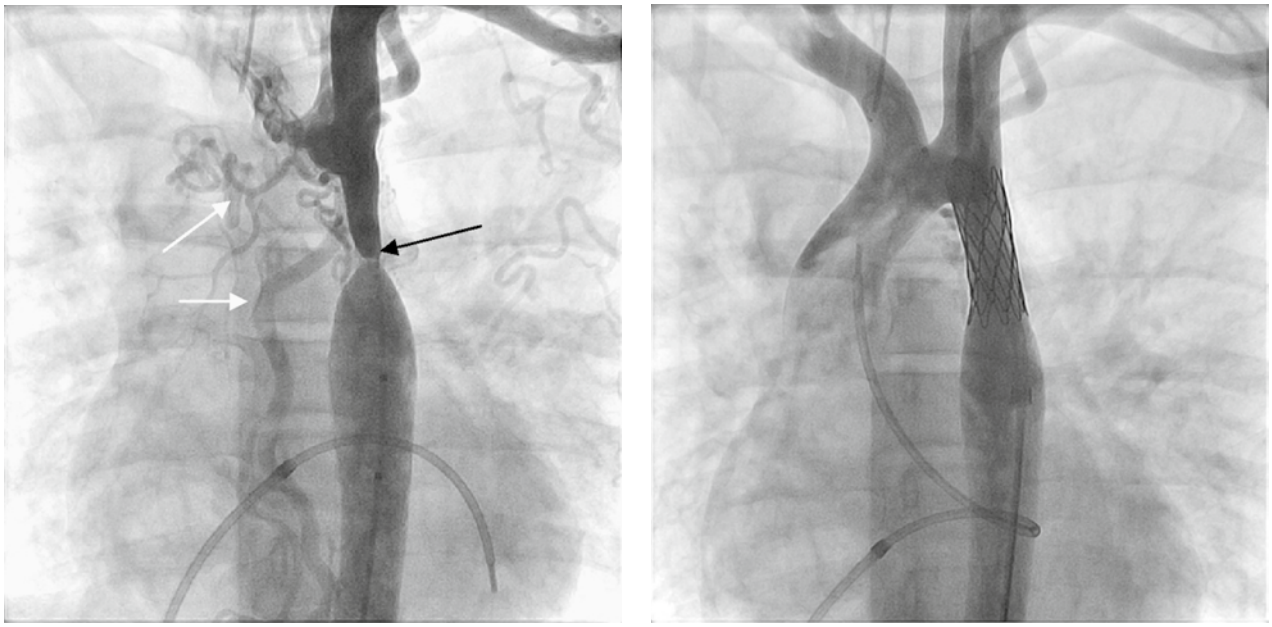


Figure 27.9 (A) Angiograms of a 12-year-old patient with a native aortic coarctation (black arrow) and a long, moderately hypoplastic isthmus before placement of a stent. Note the multiple arterial collaterals (white arrows). (B) Angiogram after stent placement. The systolic gradient was reduced from 30 to 3 mmHg following stent placement. (Source: Robert Beekman, MD. Reproduced with permission.)

[112–115] (Figure 27.9). In a study including 565 procedures from multiple institutions, 97.9% of patients had a successful reduction in the coarctation gradient at the time of the procedure [112]. Stents have been successfully used to treat patients with both discrete coarctation and transverse arch hypoplasia. Intermediate follow-up in patients receiving stents shows that the incidence of restenosis is reduced compared to balloon angioplasty [113–115]. Stents allow for future redilation to a larger size to accommodate the growth of the child. This therapy is limited by the need for a large sheath (8–9 Fr) in the femoral artery, and is thus not utilized in some centers until a child reaches a certain size. Endovascular stents have been placed in smaller children using the carotid artery, thus requiring a surgical procedure to place a sheath in this vessel. Complications related to stent placement include aneurysm formation, aortic dissection, stent migration, balloon rupture, femoral artery injury, and stroke, and may occur in as many as 15% of patients [116]. The use of covered stents, currently investigational in the United States, may decrease the risk of arterial wall injury, particularly in older patients with increased aortic fragility. In a recent single-center study, 56 patients (11–56 years of age) were treated with covered stents for complex coarctation of the aorta with a decrease in the systolic gradient from a mean of approximately 50 to around 5 mmHg [117]. Complications included one patient who was found to have an aortic dissection, which was treated conservatively, and one death during the postoperative period felt to be related to pre-existing left ventricular dysfunction. Redilation of the stent due to a subsequent increase in the gradient was required in four patients.

Anesthetic considerations

The medical management of infants with severe coarctation consists of inotropic support and diuretics. In infants younger than 1 month, intravenous prostaglandin is utilized to reopen the ductus arteriosus. Intubation may be necessary to decrease the work of breathing and reduce left ventricular demand. Metabolic acidosis should be corrected to improve left ventricular function.

The anesthetic management of the patient presenting for surgical repair of coarctation of the aorta should include a right-sided upper extremity arterial catheter in addition to the usual anesthetic monitors. The placement of the right intra-arterial catheter ensures that blood pressure will be monitored during the phase of the operation when the aorta, left carotid artery, and left subclavian artery may be clamped or compressed. The use of cerebral near-infrared spectroscopy (NIRS) for continuous monitoring of bi-hemispheric cerebral oxygenation allows the anesthesiologist to identify cerebral hypoperfusion related to aortic cross-clamp position or inadequate cardiac output [118]. Central venous access may be indicated for initiation of inotropic support.

Induction of anesthesia can be accomplished by either intravenous or inhalational anesthesia; however, in the child with significant ventricular dysfunction, an opioid-based induction may be preferable. The surgical repair is usually performed through a left thoracotomy, and lung retraction can impact ventilation. Single lung ventilation, especially in larger children, can facilitate access to the aorta. (See Chapter 23 for further discussion of single lung ventilation). Close monitoring of arterial blood gases for adequacy of ventilation is vital. Inadequate ventilation causing severe acidosis in a critically ill

neonate can worsen cardiac function and lead to cardiac arrest. There have been reports that infants with a core temperature greater than 38 °C are at an increased risk for spinal cord ischemia. Many centers choose to allow the child to cool to about 34–35 °C in order to protect against this complication [119]. The application of the aortic cross-clamp usually causes upper body hypertension. This increase in arterial blood pressure is important for maintenance of blood flow to the lower body and spinal cord which is reliant on collateral flow that can vary depending on the anatomy of collateral blood vessels and arterial pressure. Some authors advocate for mainting upper extremity blood pressures of 100–120 mmHg in infants and 160–200 in older patients during this clamp period [120]. It is possible that the failing ventricle may be unable to maintain an appropriate cardiac output after cross-clamp placement due to the sudden increase in afterload, in which case an inotropic agent may need to be administered [121]. If myocardial function is adequate, volatile anesthetics can be used to reduce the arterial pressure during aortic cross-clamp. When aortic coarcation repair is performed in older children and adults, some centers advocate for placement of a lower extremity arterial line and maintenance of a mean arterial pressure >45 mmHg. If this pressure cannot be maintained the use of left heart bypass may be indicated. Prior to completion of the vascular anastomosis, the dose of volatile anesthetic is usually reduced and fluid boluses may be administered in anticipation of systemic hypotension following release of the aortic cross-clamp.

The early postoperative period is often complicated by the onset of hypertension, which may be exacerbated in the setting of poor pain control. Greater than one-half of patients who undergo repair of a coarctation experience significant increases in blood pressure for up to 2 weeks [122]. It has been postulated that the increase in blood pressure may be secondary to stimulation of the sympathetic system distal to the anastomotic site, with subsequent increases in plasma renin activity. Untreated hypertension can result in mesenteric arteritis [123]. Hypertension in the acute perioperative period is usually treated with infusions of sodium nitroprusside, nicardipine, or esmolol. Some centers utilize continuous epidural analgesia for control of pain following coarctation repair. Purported benefits of this technique compared with intravenous opioid therapy include better pain and blood pressure control and improved respiratory mechanics. Others avoid epidural analgesia because of the potential for confusion as to etiology in the rare instance of paraplegia after coarctation repair.

KEY POINTS: COARCTATION OF THE AORTA

- Coarctation of the aorta is commonly located immediately distal to the takeoff of the left subclavian artery and may be accompanied by hypoplasia of the transverse aortic arch.
- Neonates with aortic coarctation may present with congestive heart failure due to left ventricular dysfunction and may require inotropic support and mechanical ventilation prior to surgical repair.
- Maintaining myocardial contractility and a higher blood pressure during the aortic repair is important to provide perfusion to the spinal cord and subdiaphragmatic viscera. In older patients invasive monitoring of lower extremity blood pressure may be indicated.
- Patients with a history of repaired aortic coarctation are at an increased risk for systemic hypertension, left ventricular systolic and/or diastolic dysfunction, and coronary artery disease.

Interrupted or hypoplastic aortic arch

Incidence, anatomy, and natural history

An interrupted aortic arch (IAA) exists in about 1% of patients with congenital malformations of the heart. The interruption may be divided into three anatomical variants: type A, which is characterized by a location just distal to the left subclavian artery (25% of IAA); type B, located in the space between the left subclavian artery and the left common carotid artery (70% of IAA); and type C, between the innominate and left common carotid arteries (5% of IAA) [123, 124] (Figure 27.10). The majority of patients with a type B IAA have DiGeorge syndrome (chromosome 22q11.2 deletion) [125]. Common features in the infant with DiGeorge syndrome include hypocalcemia, an absent thymus, and anomalies of the ears, face, and palate.

All types of IAA have a high incidence of associated congenital cardiac anomalies. A VSD is most prevalent and present in greater than 90% of type B interruptions and more than 50% of type A interruptions [126]. The VSD is usually posteriorly malaligned, leading to posterior deviation of the conal septum into the LVOT. Other concomitant cardiac defects include bicuspid aortic valve, truncus arteriosus, transposition of the great arteries, and double outlet right ventricle [127]. LVOT obstruction occurs in as many as 57% of patients with IAA, and is more commonly associated with type B interruption and anomalous right subclavian artery (Table 27.6) [128, 129].

In children born with IAA, the prognosis for survival without surgical intervention is poor, with as many as 90% of patients dying within the first year of life [130]. Those who survive past the first year develop a collateral circulation that allows for adequate lower-body perfusion despite the aortic interruption [131]. Even with surgical intervention during infancy, many children will require subsequent procedures later in life and should be closely followed by a congenital cardiologist [132]. The most common indications for surgical- or catheter-based interventions following IAA repair are aortic arch obstruction and LVOT obstruction [133].

Pathophysiology

Neonates suffering from IAA often remain asymptomatic initially after birth, but over the course of a few days or weeks, they can become precipitously ill following closure of the ductus arteriosus. As the duct constricts, blood flow to the lower body becomes compromised, drastically increasing the risk of shock. Congestive heart failure may develop as a greater proportion of blood flow is directed to the

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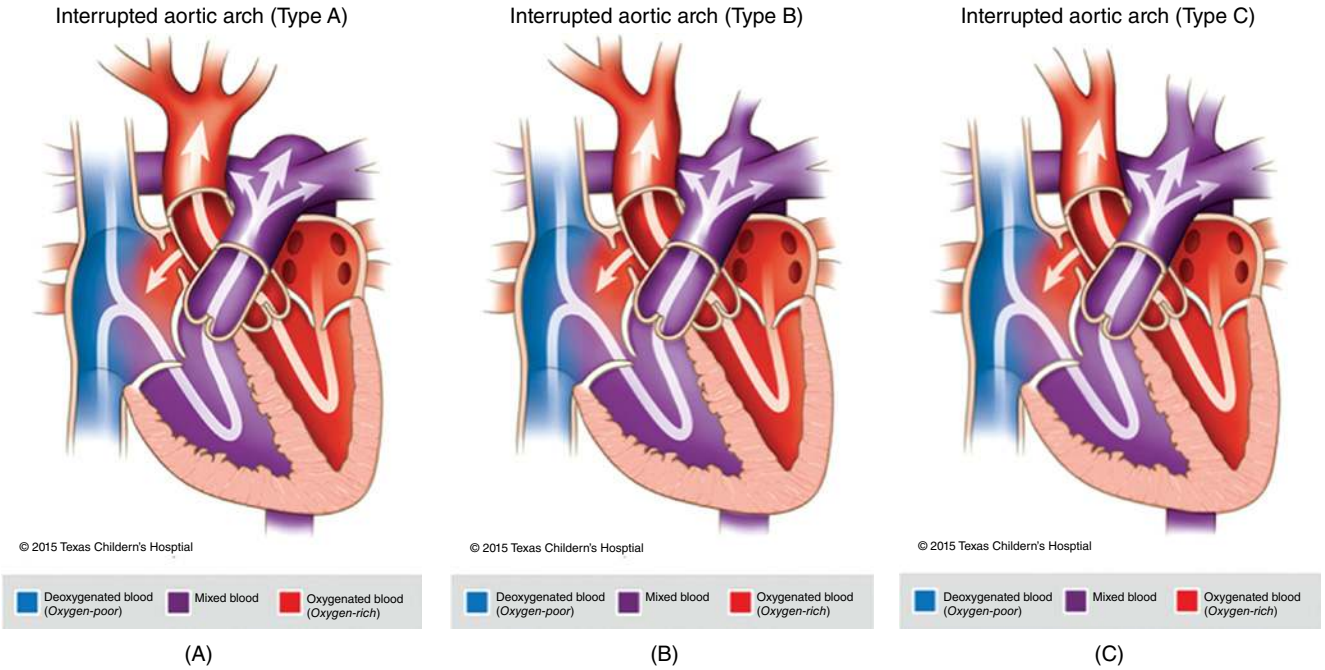


Figure 27.10 Interrupted aortic arch. (A) Type A: interruption between the left subclavian artery and the ductus arteriosus. (B) Type B: interruption between the left carotid and left subclavian arteries. (C) Type C: interruption at the proximal aortic arch between the innominate and left carotid arteries. (Source: Reproduced with permission from Texas Children's Hospital.)

Table 27.6 Demographic and anatomic features associated with interrupted aortic arch

Variable	No.	Missing	Value	Deaths (*n* = 186)
Demographic characteristics				
Age at admission (d, median and range)	468	4	3 (birth-30)	
Demographic characteristics				
Age at admission (d, median and range)	468	4	3 (birth-30)	
Birth weight (kg, mean ± SD)	190	282	3.04 ± 0.64	
Sex (female/male)	471	1	234:237	80:106
Noncardiac anomaly (No.)	472	0	165 (35%)	68 (41%)
DiGeorge syndrome (No.)	472	0	86 (18%)	33 (38%)
Morphologic characteristics (No.)				
Type of IAA				
Type A	468	0	130 (28%)	33 (26%)
Type B	468	0	331 (70%)	144 (44%)
Type C	468	0	7 (1%)	7 (100%)
Major associated cardiac anomalies				
None – isolated VSD	472	0	341 (72%)	121 (35%)
None – intact ventricular septum	472	0	7 (1%)	2 (29%)
Aortopulmonary window	472	0	20 (4%)	3 (15%)
Complete atrioventricular septal defect	472	0	3 (<1%)	3 (100%)
Atrioventricular discordance	472	0	2 (<1%)	1 (50%)
Double-outlet right ventricle	472	0	8 (2%)	4 (50%)
Partial anomalous pulmonary venous return	472	0	1 (<1%)	1 (100%)
Single ventricle	472	0	13 (3%)	9 (69%)
Transposition of great arteries with VSD	472	0	26 (6%)	9 (35%)
Truncus arteriosus	472	0	51 (11%)	34 (67%)
Bicuspid aortic valve	229	243	149 (65%)	57 (38%)
Anomalous right subclavian artery	427	45	108 (25%)	45 (42%)
Left superior vena cava	440	32	35 (8%)	19 (54%)
Large patent ductus arteriosus	281	191	251 (89%)	94 (37%)
Large VSD	392	80	322 (82%)	123 (38%)
Multiple VSDs	383	89	31 (8%)	14 (45%)
Malalignment of VSD	472	0	165 (35%)	74 (32%)

Source: Data from Oosterhof et al. [127].

pulmonary circulation. Rapid diagnosis accompanied by initiation of prostaglandin therapy, treatment of metabolic acidosis, and respiratory and/or myocardial support may be lifesaving. Fetal echocardiography has led to improvements in early diagnosis and a reduction in the number of neonates presenting with circulatory collapse. Unlike the neonate with severe coarctation of the aorta, differential oxygen saturations between the right upper and lower extremities may not be present due to mixing of blood through a VSD.

The diagnosis of IAA can usually be established with TTE, and cardiac catheterization is usually not indicated. MRI and CT angiography have also been used to delineate complex arch anatomy. Careful evaluation for additional cardiac anomalies, including the presence of LVOT obstruction, is important.

Surgical and transcatheter approaches and outcomes

Surgical strategies for treatment have varied. A two-stage approach involving initial repair of the aortic arch through a left thoracotomy accompanied by pulmonary artery banding allows for palliation without the use of CPB. This approach provides only limited exposure of the proximal aorta and does not allow the surgeon to address other coexisting lesions such as LVOT obstruction. A primary one-stage repair using a midline sternotomy and CPB is now favored. This approach provides optimal exposure for aortic arch repair, and the ability to close the VSD and address other associated lesions. One multicenter study suggested that surgical approaches other than direct anastomosis with patch augmentation of the IAA may increase the risk for future aortic arch reintervention [23]. However, a subsequent study reported that 100% of patients required no arch reintervention at 5 years after direct anastomosis without patch augmentation when the descending thoracic aorta was circumferentially mobilized, ductal tissue aggressively excised, and a wide anastomosis made between the descending aorta and the posterior aspect of the distal ascending aorta [134]

In the setting of IAA with VSD and severe LVOT obstruction, an alternative surgical plan may be indicated. Alternative surgical strategies in the setting of severe LVOT obstruction include the Yasui procedure, which combines the interrupted arch repair with a Damus-Kaye-Stansel (DKS) [135]. A VSD patch baffle is utilized to connect the left ventricle to the DKS root and a right ventricle to pulmonary artery conduit is placed to provide pulmonary blood flow (Figure 27.11) [136]. This operation can be performed as the primary repair during the neonatal period or as a staged procedure in which a Norwood operation is the initial surgery. Another alternative strategy is to perform the Ross-Konno procedure as the initial procedure or as subsequent operation for relief of LVOT obstruction.

Until the last decade, major aortic arch surgery required the use of deep hypothermia with circulatory arrest, which may adversely impact long-term neurodevelopmental outcomes [137]. Many centers now use antegrade cerebral (ACP) and myocardial perfusion during arch repair providing continuous delivery of oxygen to the brain and minimizing myocardial ischemic time (see Chapter 11). Over the next decade, studies should elucidate whether these techniques improve survival and reduce long-term morbidities.

Interrupted aortic arch continues to be associated with significant mortality during the perioperative period and subsequent long-term follow-up. A study reporting outcomes from 33 institutions between 1987 and 1997 found an overall survival of 60% at 21 years after initiation of study [132]. One-third of patients in this study required one or more subsequent arch and/or LVOT procedures. Other studies found an overall perioperative mortality rate for procedures done since 1990 of 12%, compared with an overall mortality rate of 42% prior to 1985 [138]. One-month survival of >92% following IAA repair has been reported at a number of centers [128, 134]. Risk factors reported to be associated with increased mortality include low birth weight, type B IAA, other major associated cardiac anomalies, DiGeorge syndrome, LVOT obstruction, and an episode of circulatory collapse prior to repair [23, 127, 134]. Several studies have questioned whether LVOT obstruction is a risk factor for increased operative mortality [130, 134].

Preoperative aortic root size has been shown to predict the need for reintervention for postoperative LVOT obstruction after single-stage repair of IAA with VSD. In a single-center study of 70 patients with IAA and VSD, 23% of patients required a reintervention for LVOT obstruction with a median time to reintervention of 1.2 years [133]. Subaortic resections were performed via a surgical approach, while aortic valve stenosis was treated with aortic balloon valvuloplasty. A recent publication recommended that in neonates with a preoperative aortic valve annulus diameter less than the patient's weight in kilograms, the risk of LVOT obstruction after standard repair is high and some type of LVOT bypass procedure should be considered [139].

Anesthetic considerations

Intravenous access will have been established in the neonate with IAA scheduled for surgery. Induction of general anesthesia is usually accomplished with an opioid and benzodiazepine in combination with a non-depolarizing muscle relaxant. Inhaled anesthetic agents can be safely used as long as blood pressure is closely monitored and maintained. Management of ventilation following anesthetic induction and intubation is aimed toward optimizing systemic cardiac output. The use of a low inspired FiO_2 and avoidance of hyperventilation reduces pulmonary overcirculation. The use of cerebral NIRS can help guide anesthetic management during this period.

The optimal position for placement of the arterial catheter requires careful consideration in the infant with IAA. The right subclavian artery may originate in an anomalous fashion from the descending aorta, especially in a type B IAA with associated subvalvular AS [140]. In one study, 15 of 49 patients with type B IAA had a coexisting anomalous right subclavian artery [128]. In some cases, the left subclavian artery may be utilized during the surgical repair. The use of an umbilical artery catheter is ideal in this setting. In the absence of an anomalous right subclavian artery, some centers prefer to have both a right upper extremity and lower body (UAC or femoral) arterial line. The right upper extremity arterial line allows for monitoring of arterial pressure to help guide flow rate during regional cerebral perfusion (See Chapter 11 for detailed discussion). Central venous access is indicated for the infusion of inotropic agents and monitoring of intracardiac pressures. This can be accomplished by either

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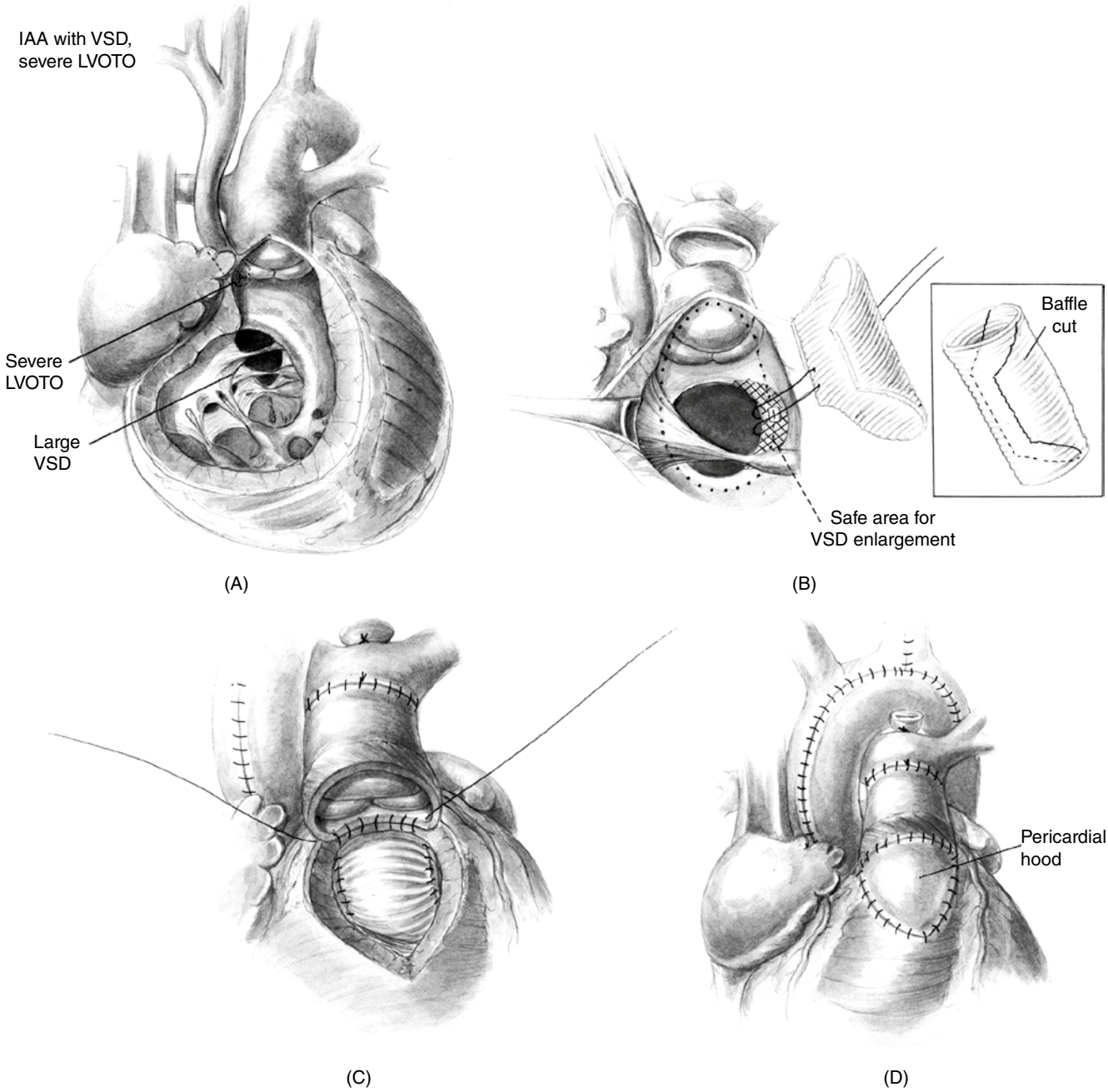


Figure 27.11 Yasui operation. (A) This depicts a cutaway of the anatomy of a patient with type B interrupted aortic arch with severe left ventricular outflow tract obstruction (IAA/LVOTO). Commonly, these patients have aberrant origin of the right subclavian artery from the descending aorta. The left ventricular outflow tract obstruction is both muscular (subvalvular) as well as due to a hypoplastic aortic annulus and ascending aorta. A standard biventricular repair of interrupted aortic arch with VSD, consisting of VSD closure and repair of the arch, could result in significant postrepair left ventricular outflow tract obstruction. Although these patients can be managed with a neonatal Ross-Konno procedure and arch repair, a Yasui operation is a useful alternative. IAA = interrupted aortic arch; LVOTO = left ventricular outflow tract obstruction; VSD = ventricular septal defect. (B) A Hemashield (Boston Scientific, Natick, MA) Dacron graft (usually 10 or 12 mm) is opened longitudinally and trimmed as shown in the inset. This is used to baffle the left ventricular outflow through the VSD to the pulmonary artery. At least half of the circumference of the graft is used to insure a generous unobstructed pathway through the VSD to the pulmonary valve. The superior tip of the baffle is typically at the most anterior portion of the right ventriculotomy and the inferior tip of the baffle is oriented just near the papillary muscle of Lancisi. A continuous 5/0 polypropylene suture is used for the majority of the baffle, keeping well on the right ventricular side of the VSD to avoid the area of the conduction tissue. The portion along the septal leaflet of the tricuspid valve is typically closed with interrupted pledgeted 5/0 polypropylene sutures with the pledgets on the atrial side of the tricuspid valve. This more easily can be done through the right atriotomy. VSD = ventricular septal defect. (C) The superior edge of the right ventriculotomy is sewn to the posterior wall of the proximal homograft with continuous 5/0 polypropylene incorporating the leading edge of the VSD patch into a portion of this anastomosis for hemostasis and security. (D) Right ventricular to homograft continuity is established with a roof of autologous pericardium using contin- uous 5/0 polypropylene to complete the repair. (Source: Reproduced with permission from Kanter [136].)

percutaneous catheterization or placement of intracardiac lines by the surgeon prior to separating from CPB. Echocardiography using a pediatric TEE probe can effectively guide inotropic and fluid management, determine the adequacy of VSD closure, and assess the LVOT for any evidence of obstruction. Two intravenous catheters should be placed, as significant blood loss may occur following separation from CPB. The use of deep hypothermia places the infant at higher risk for significant bleeding after CPB; red blood cells, platelets, and cryoprecipate should be available. In the case of the infant with DiGeorge syndrome, the use of irradiated blood is necessary to avoid graft-versus-host reactions [141].

Separation from CPB usually requires inotropic support and close monitoring of serum calcium levels. The infant with DiGeorge syndrome is prone to hypocalcemia and may benefit from a calcium infusion. Once the hemodynamics are stabilized and the bleeding is controlled, sternal closure may be attempted. Inotropic support, fluid management, and ventilation may need to be adjusted at this time. The patient should be closely monitored for pulmonary hypertension following repair and, if present, may benefit from inhaled nitric oxide. Should sternal closure result in unacceptable instability due to a reduction in cardiac output or pulmonary function, a polytetrafluoroethylene patch may be placed over the open chest for subsequent closure in 1–3 days.

KEY POINTS: INTERRUPTED OR HYPOPLASTIC AORTIC ARCH

- 70% are type B (L common carotid-subclavian artery; 90% VSD), 25% type A (distal to L subclavian artery; 50% VSD), 5% type C (innominate-left common carotid)
- Another important associated cardiac finding in the child with an interrupted arch includes LVOT obstruction.
- Neonates with an IAA or severely hypoplastic aortic arch are dependent on patency of the ductus arteriosus for blood flow to major abdominal organs and the lower extremities.
- IAA should be considered a chronic disease for which future interventions on the aortic arch and/or LVOT are common.
- Management of ventilation prior to CPB includes the use of a low inspired FiO_2 and avoidance of hyperventilation to increase pulmonary vascular resistance.

Shone's anomaly

Incidence, anatomy, and natural history

Shone's anomaly (or Shone's complex) consists of a supravalvular mitral ring, parachute deformity of the mitral valve, subvalvular AS, and coarctation of the aorta, and was first described by Shone and colleagues in 1963. This complex of lesions causes multi-level left heart obstruction and is variable in regard to the presence and severity of each lesion [142, 143]. In 30 consecutive patients with Shone's anomaly, 73% had a supravalvular mitral ring, 87% had a parachute mitral valve, 87% had subvalvular AS, and 97% had coarctation of the aorta. Additional lesions also present in these patients were a bicuspid aortic valve (61%) and a VSD (67%) [142]. Hypoplasia of the left ventricle is generally not considered a component of Shone's complex. The parachute mitral valve describes a mitral valve deformity where two mitral valve leaflets are supported by only one papillary muscle and the chordae are usually shortened and thickened [144] (Figure 27.12). Because the mitral leaflets are pulled together in proximity, the mitral valve can become stenotic. The supravalvular ring is a ridge of connective tissue arranged circumferentially on the atrial side of the mitral leaflets. Although this ring does not cause severe obstruction in the majority of cases, fibrous tissue can obtrude into the mitral inflow tract, causing obstruction. Although not classically considered part of Shone's anomaly, "typical" congenital mitral stenosis with a small annular size has been noted in 25–50% of patients with Shone's anomaly in two published series [145, 146]. Subvalvular AS is caused by either a discrete membranous thickening in the outflow tract or a more complex long-segment "tunnel" stenosis. The coarctation is usually located in the descending aorta in proximity to the left subclavian artery.

Cor triatriatum must also be considered in the setting of left-sided obstructive disease. The anomaly is characterized by the pulmonary venous return entering an accessory left-sided chamber that connects with the left atrium through a slender passageway (Figure 27.13). The left atrial appendage and fossa ovalis are always distal to the obstructing membrane. In contrast, a supramitral stenosing ring, when present as part of Shone's complex, leaves the left atrial appendage in connection with the upper portion of the left atrium and proximal to the stenosing formation [147].

The natural history of Shone's anomaly is highly variable and dependent on the severity of the left-sided obstructive lesions and the degree to which the obstructive lesions can be relieved. In particular, the degree of involvement of the left ventricular inflow tract is the major factor, which determines long-term outcome. In a recent study of 45 children with Shone's anomaly, the cumulative survival rate was 70% at 15 years following mitral valve repair, and risk factors for reoperation and mortality included the severity and type of mitral valve abnormalities, LVOT lesions, and pulmonary hypertension [148]. In another large retrospective single-center study which followed 121 patients with Shone's syndrome and a biventricular circulation, the transplant-free survival was 86% [139]. These children required multiple surgical and catheter-based interventions but showed significant left heart growth over the study period.

Pathophysiology

Patient symptoms depend on the anatomic location of the most critical areas of obstruction. As many as two-thirds of patients with Shone's anomaly may present in the neonatal period with an aortic coarctation [146]. Assessment of the hemodynamic significance of lesions causing obstruction of the mitral valve or subaortic region can be very challenging in the context of a ductal-dependent systemic circulation. After the repair of aortic coarctation, these infants are followed closely for signs of congestive heart failure often

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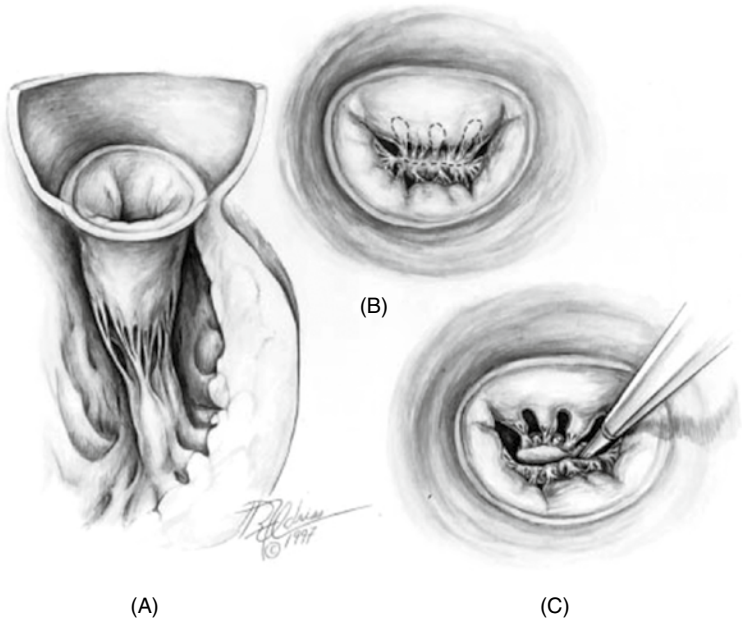


Figure 27.12 Cut-away atrioventricular view (A) and left atrial views (B, C) of a stenotic parachute mitral valve. (A) A single papillary muscle or fused papillary muscles usually arise from the posterior left ventricular wall. (B) The dotted lines show the areas of proposed leaflet fenestrations and papillary muscle incision to open the ven- tricular inlet. (C) Leaflet fenestrations are accomplished to maximize unrestricted blood flow into the left ventricle during diastole while preserving enough valvular tissue for effective coaptation during systole. The fused papillary muscle is being incised to facilitate valvular mobility. (Source: Zias et al. [144]. Reproduced with permission from Elsevier.)

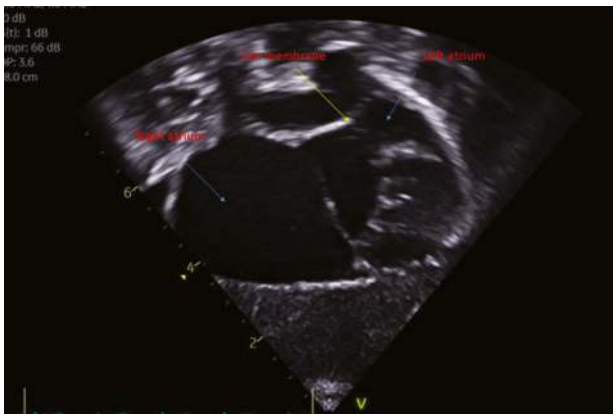


Figure 27.13 Tranthoracic echocardiograpohic image of a patient with Cor Triatriatum. (Source: Courtesy of Michael Taylor, MD.)

related to mitral valve abnormalities. Subvalvular AS is rarely significant in the neonatal period but can rapidly progress during infancy [47]. Those patients with a high degree of subvalvular AS will develop left ventricular hypertrophy.

Echocardiography and cardiac catheterization with angiography are the primary diagnostic modalities for detecting and defining the extent of the Shone's anomaly [149]. The presence of markedly elevated pulmonary vascular resistance at cardiac catheterization increases perioperative risk and worsens long-term outcome. It is extremely important to be aware of all levels of obstruction, because the intraoperative repair of one obstruction may often reveal other less critical stenoses that continue to impede blood flow. Failure to recognize all levels of obstruction leads to increased perioperative risk for the patient.

Surgical and transcatheter approaches and outcomes

The intracardiac surgical repair generally consists of resection of the supravalvular mitral ring, fenestration of the mitral valve tensor apparatus, repair or replacement of the mitral valve, and resection of any encroaching muscular tissue in the LVOT. When aortic arch obstruction is present, surgical repair of this lesion may be necessary during the neonatal period. Early mitral valve repair is advocated whenever possible, allowing for continued annular growth and avoidance of anticoagulation, and should occur before pulmonary hypertension develops [146]. When subvalvular AS is caused by a discrete membranous lesion, resection is performed through a transaortic approach and accompanied by ventricular septal myectomy, which is felt to reduce the incidence of recurrence [150]. A long-segment "tunnel" type of subvalvular AS is commonly corrected with an aortoventriculoplasty (Konno procedure) [151] (Figure 27.14). The Konno operation is used to augment the left ventricular outflow tract and enlarge the aortic annulus and requires placement of a prosthetic aortic valve or a pulmonary autograft (Ross-Konno) [152] (Figure 27.15). The modified Konno operation is performed when the aortic annulus is normal in size and placement of a prosthetic valve in the aortic position is not necessary [153, 154]. Intraoperative TEE is important for anatomic assessment before CPB and then following surgical repair. Surgical and long-term outcomes for Shone's anomaly depend on the age of

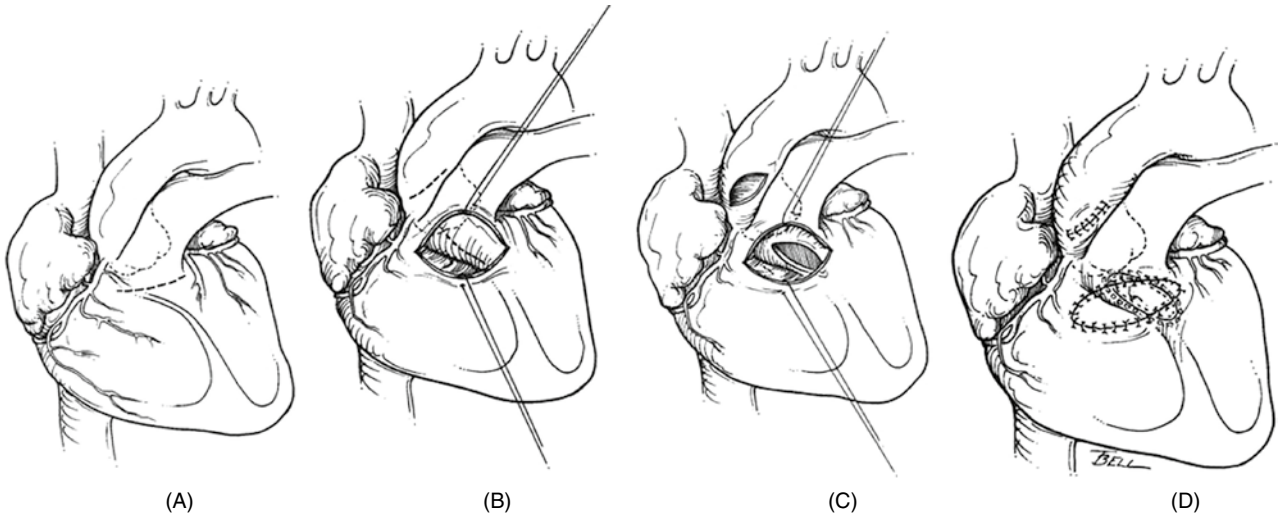


Figure 27.14 The modified Konno operation. (A, B) Incisions are made in the ascending aorta (to assess outflow and protect aortic valve), infundibulum, and conal septum. (C, D) The outflow is enlarged with a polytetrafluoroethylene patch, and the infundibulotomy is also closed with a patch. (Source: Takahashi & Hanzawa [151]. Reproduced with permission from Springer Nature.)

presentation, severity of mitral valve disease, need for multiple surgical procedures, and presence of pulmonary hypertension [142, 145, 146]. Despite an initially satisfactory mitral valve repair, approximately one-half of children with Shone's anomaly will require a subsequent repair or mitral valve replacement [148].

Diagnostic cardiac catheterization is often indicated in patients with Shone's anomaly to better assess the relative hemodynamic significance of multi-level left-sided obstructive lesions and the degree of pulmonary hypertension. Catheter-based interventions may also be indicated to address primary or recurrent aortic arch obstruction.

Anesthetic considerations

The medical management of patients with Shone's complex depends on the location of the most critical stenosis. Neonates with coarctation of the aorta will require prostaglandins to maintain patency of the ductus arteriosus and appropriate ventilatory strategies aimed at reducing pulmonary overcirculation. Children with dynamic LVOT obstruction may require β-blockers to improve intracavitary laminar blood flow. Congestive heart failure is usually treated with diuretics and may require inotropic support. The presence of pulmonary hypertension before or after surgery for relief of a left sided obstructive lesion may require a phosphodiesterase inhibitor (such as milrinone) and nitric oxide [155, 156]. In the presence of a significant left-sided obstructive lesion, the effects of nitric oxide can be variable, and this drug should be used with caution.

The anesthetic management of the patient with Shone's anomaly requires an appreciation of all levels of stenosis and knowledge of the location of the dominant lesion. A patient with predominantly mitral stenosis requires sufficient preload to maintain left atrial pressure, and a normal to slow heart rate to optimize ventricular filling during diastole. In the patient primarily suffering from subvalvular AS and left ventricular hypertrophy, arterial pressure needs to be maintained for optimal myocardial perfusion. An anesthetic plan carefully tailored to meet these hemodynamic goals is vital for optimal outcome.

KEY POINTS: SHONE'S ANOMALY

- Shone's anomaly consists of multiple left-sided obstructive lesions, including a supravalvular mitral ring, parachute deformity of the mitral valve, subaortic stenosis, and coarctation of the aorta.
- The presence of multiple levels of obstruction can make assessment of the degree of obstruction at each level extremely challenging.
- Important principles of anesthetic management include maintaining sufficient preload, a normal to slow heart rate to optimize ventricular filling, and maintaining arterial blood pressure to assure optimal myocardial perfusion.

Mitral stenosis

Incidence, anatomy, and natural history

Mitral stenosis is most often observed as a component of a complex left-sided malformation syndrome, i.e., Shone's anomaly. Isolated congenital mitral valve stenosis is a rare lesion, occurring in well less than 1% of infants with CHD and a normal-sized left ventricle [157]. The anatomical complexity of the mitral valve and its supporting apparatus, the papillary muscles and chordae tendineae, have led to several complicated schemata to describe abnormalities of the mitral valve [157–159]. One functional classification of mitral stenosis anatomy divides this lesion into type A, with a normal papillary muscle, which includes commissural fusion, a

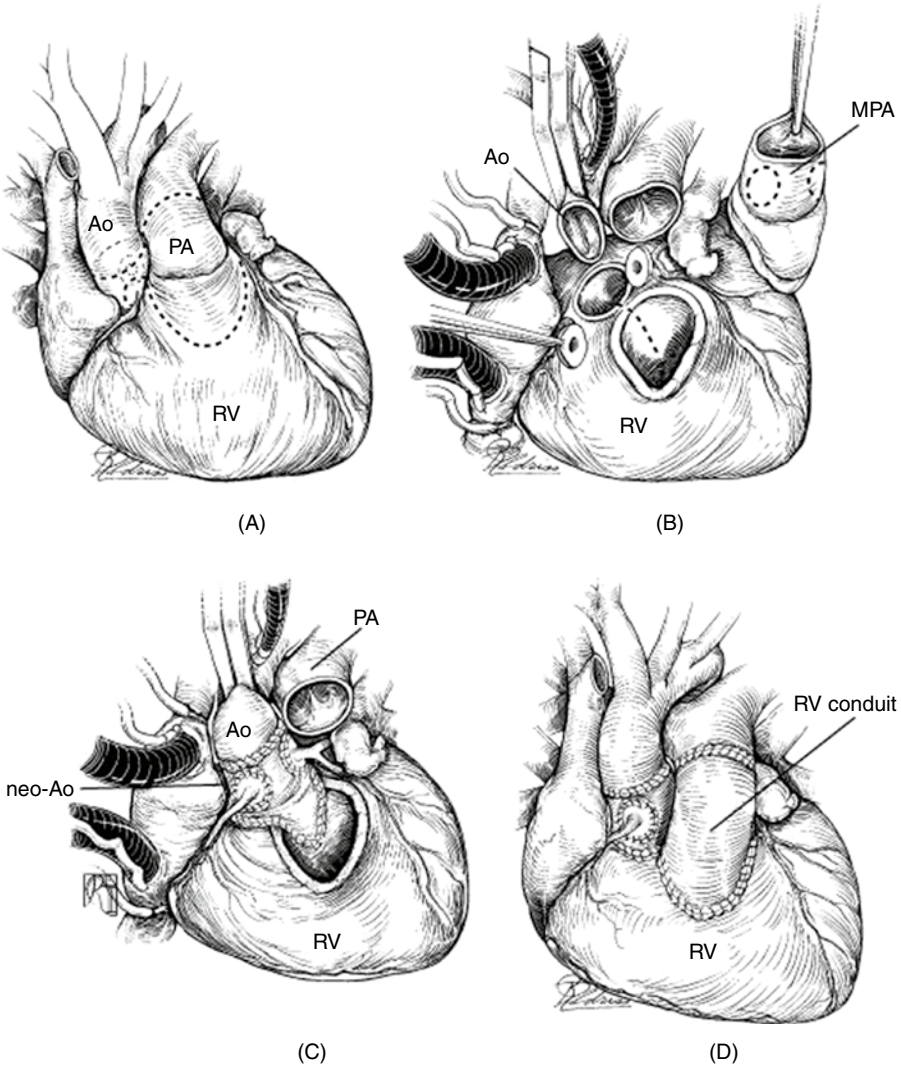


Figure 27.15 Ross-Konno operation. (A) Intended incision and excision boundaries en route to the Ross-Konno Procedure. (B) After aortic cross-clamping, antegrade and retrograde cardioplegic arrest, aortic resection, coronary mobilization, and main pulmonary artery harvest, the inter ventricular incision is noted by the dotted line. The pulmonary autograft was harvested, with an extra portion of right ventricle to be used for the ventriculoseptoplasty part of this operation. (C) The neoaortic left ventricular outflow recontruction is shown using the pulmonary autograft extension into the interventricular septum ("apron extension"). (D) The completed Ross-Konno procedure is shown after separation from cardiopulmonary bypasss. Ao, aorta, aortic; MPA, main pulmonary artery; PA, pulmonary artery; RV right ventricle. (Source: Tchervenkov et al. [152]. Reproduced with permission from John Wiley & Sons.)

valvular or supravalvular ring, or an obstructive left superior vena cava, and type B, which consists of an abnormal papillary muscle producing a parachute, or a hammock mitral valve. [159]. The natural history of mitral valve stenosis is dependent on the severity of the stenosis and the feasibility of repair or replacement.

Pathophysiology

Depending on the degree of mitral stenosis, a progressive elevation in left atrial pressure can lead to pulmonary venous and then pulmonary arterial hypertension. This can result in interstitial pulmonary edema, "cardiac asthma," frequent respiratory infections, tachypnea, poor feeding and poor growth. Significant pulmonary hypertension will be accompanied by elevated right ventricular pressures, right ventricular hypertrophy, and potentially diminished function. Left-sided cardiac output will be restricted by diminution of blood flow into the left ventricle. A resultant tachycardia shortens diastolic filling time and can severely depress systemic cardiac output. Hypovolemia reduces left ventricular end-diastolic volume and pressure, worsening the functional mitral stenosis. In patients with elevated pulmonary artery pressure and resistance, maneuvers to reduce PVR may paradoxically worsen the obstructive pulmonary symptoms by promoting increased pulmonary blood flow in the face of a fixed downstream obstruction. A frequently dilated left atrium predisposes to atrial arrhythmias such as atrial flutter, atrial fibrillation, or atrial tachycardia.

Anatomical diagnosis of mitral stenosis is often based solely on echocardiographic findings. Three-dimensional echocardiography is particularly useful in defining the morphological complexity of the diseased mitral valve and its use is increasingly widespread [160, 161]. Decisions about

intervening are made on the basis of increasing clinical symptomatology, such as frequent respiratory infections and failure to thrive despite optimal medical management.

Surgical and transcatheter approaches and outcomes

When surgery is indicated, most congenital heart surgeons adopt a conservative approach, repairing the stenotic valve whenever possible [162]. There are a number of techniques employed, including resection of a supravalvular ring, commissurotomy, division or reconstruction of the papillary muscles, and reconstruction of the chordae tendineae [159, 162]. The main goal of surgery is to reduce the mitral stenosis without producing mitral regurgitation; the surgeon will often perform a test of the repair with the aorta cross-clamped by rapidly instilling saline solution through the repaired valve to produce a normal end-diastolic volume. Retention of this volume in the left ventricle signifies lack of significant mitral regurgitation. After separation from bypass, TEE is critical in assessing the adequacy of repair and the need for returning on bypass to improve the surgical result. Because of the potential morbidity from anticoagulation and the need for future replacement as a child grows, mitral valve replacement is performed only as a last resort in young children, when attempts at repair have failed. However, when a mitral valve repair cannot be successfully performed in these patients, a supra-annular mitral valve replacement may be necessary in infants because of the small size of the annulus. Surgical outcomes are dependent on the specific abnormality and the feasibility of repair. The need for mitral valve replacement increases the risk of both short- and long-term complications. In some cases, interventional catheter approaches have been successfully used to dilate a stenotic mitral valve [163].

Anesthetic considerations

Hemodynamic goals in mitral stenosis include maintaining a low-normal heart rate to enhance diastolic filling time for the left ventricle and maintaining preload to minimize the functional stenosis across the valve. Preserving ventricular contractility and afterload are important goals of any technique. Maintaining normal sinus rhythm is critical; therefore, prompt recognition and treatment of atrial dysrhythmias are important. With severe mitral stenosis, the patient will have significant pulmonary hypertension and care must be taken not to induce a pulmonary hypertensive crisis, e.g., due to a large catecholamine surge secondary to inadequate anesthetic depth. On the other hand, acutely lowering PVR with excessive FiO_2 and hyperventilation will promote excessive pulmonary blood flow, often leading to worsening pulmonary function due to the fixed downstream obstruction at the level of the mitral valve.

During surgical repair, the left side of the heart will by necessity be opened, and there is the potential for retention of significant air in the heart during weaning from bypass. Accordingly, prolonged cardiac de-airing maneuvers, assisted by TEE, may be required. Some surgeons will insufflate CO_2 into the surgical field to improve the dissolution of any gas retained in the left side of the heart [164].

After bypass, a left atrial and possibly a pulmonary artery catheter may be placed by the surgeon. It is important to realize that pulmonary artery pressures may not be immediately reduced, and treatment with adequate depth of anesthesia and analgesia, milrinone, nitric oxide, high FiO_2, and mild hyperventilation may be required for hours or days. Left atrial pressure should decrease with successful mitral valve repair in the face of normal left ventricular function. TEE is crucial to assess the immediate results of the surgical repair.

Cor triatriatum

Cor triatriatum is a rare anomaly seen in about 0.1% of patients with CHD, consisting of a membrane or diaphragm in the left atrium, functionally dividing it into two chambers, where the pulmonary veins enter superior to the membrane [165] (Figure 27.13). Blood flows from the upper to the lower left atrial chamber through one or more orifices, and the patient's symptoms and presentation depend on the degree of restriction of blood flow through these orifices, and can range from completely asymptomatic to severely restricted blood flow. This may result in severe left atrial hypertension, pulmonary venous and arterial hypertension, and low cardiac output, similar to that seen in severe mitral stenosis. Pulmonary symptoms such as wheezing are prominent and may be the only presenting complaint [166]. Most patients present in the first year of life, and 24–80% have associated cardiac anomalies such as anomalous pulmonary venous drainage, left superior vena cava, or HLHS. The surgical approach consists of resecting the membrane in the left atrium and repairing associated defects. Anesthetic considerations are identical to those for the patient with mitral stenosis.

KEY POINTS: MITRAL STENOSIS/COR TRIATRIATUM

- Hemodynamic goals include slow-normal heart rate, and maintenance of normal sinus rhythm and adequate preload and afterload.
- Severe obstruction from these lesions can result in significant left atrial hypertension, and pulmonary venous and arterial hypertension, which may need to be managed with inhaled nitric oxide after surgical repair.
- In the face of severe obstruction pre-bypass, nitric oxide and other maneuvers to decrease PVR can worsen the problems because they do not address the anatomic obstruction.

Selected references

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart

11 Vlahos AP, Marx GR, McElhinney D, et al. Clinical utility of doppler echocardiography in assessing aortic stenosis severity and predicting need for intervention in children. Pediatr Cardiol 2008;29:507–14. Comparison of echocardiographic and cardiac catheterization data in children with isolated valvular aortic stenosis to determine the

optimal echocardiographic methodology for predicting the need for intervention.

19 Sachdeva S, Kuhn E, Frommelt PC, Handler S. Role of echocardiographic scoring systems in predicting successful biventricular versus univentricular palliation in neonates with critical aortic stenosis. Cardiol Young 2020;30:1702–7. Comparing the utility of different scoring systems to predict successful biventricular repair of severe aortic stenosis.

23 McCrindle BW, Tchervenkov CI, Konstantinov IE, et al. Risk factors associated with mortality and interventions in 472 neonates with interrupted aortic arch: a congenital heart surgeons society study. J Thorac Cardiovasc Surg 2005;129:343–50. A Congenital Heart Surgeons Society Study looking at oucomes following interrupted aortic arch repair.

40 Buratto E, Konstantinov IE. Aortic valve surgery in children. J Thorac Cardiovasc Surg 2021;161:244–50. Review of surgical treatment options for aortic stenosis and their outcomes.

52 Gray JC, 3rd, Krazinski AW, Schoepf UJ, et al. Cardiovascular manifestations of Williams syndrome: imaging findings. J Cardiovasc Comput Tomogr 2013;7:400–7. Contemporary review of imaging findings of cardiovascular manifestations of Williams syndrome, a disease with significantly increased prevalence of cardiac events and sudden death.

72 Monda E, Rubino M, Lioncino M, et al. Hypertrophic cardiomyopathy in children: pathophysiology, diagnosis, and treatment of non-sarcomeric causes. Front Pediatr 2021;9:1–19. A contemporary review of hypertrophic cardiomyopathy in children.

104 Gropler MRF, Marino BS, Carr MR, et al. Long-term outcomes of coarctation repair throught left thoracotomy. Ann Thorac Surg 2019;107:157–64. A single center retrospective review of surgical outcomes after coarctation repair and the impact of transverse arch hypoplasia on surgical approach.

116 Ammar RI. Balloon angioplasty for native aortic coarctation in children and infants younger than 12 months: immediate and medium-term follow-up. J Invasive Cardiol 2012;24:662–6. Immediate and medium-term outcomes for balloon angioplasty of native aortic coarctation in infants <12 months of age.

148 Delmo Walter EM, Van Praagh R, Miera O, et al. Repair of left ventricular inflow tract lesions in Shone's anomaly: valve growth and long-term outcome. Ann Thorac Surg 2013;95:948–55. Retrospective study of 45 chidren with Shone's anomaly demonstrating that long-term functional outcomes best correlate with successful mitral valve repair.

CHAPTER 28
Anesthesia for Right-Sided Obstructive Lesions

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Introduction

Right-sided obstructive congenital heart disease (CHD) is extremely variable in presentation – both in severity and clinical signs and symptoms. In some cases, severe cyanosis and/or congestive heart failure (CHF) is immediately apparent in a neonate, whereas in other cases, a teenager or adult may present with mild complaints of fatigue or reduced exercise ability. Variations in the extent of malformations in the right heart and great vessels dictate the severity and timing of presentation. All right-sided obstructive diseases can cause right-to-left shunting of blood flow.

Obstruction to blood flow in the right heart can result from malformations at a single anatomical area, such as the right atrioventricular (AV) valve, or multiple structural sites, as found in the tetralogy of Fallot (TOF). Failure of tissue formation and coordinated growth leads to poor development of valvar structures and incomplete septation of the right heart from the left. Impairment of normal hemodynamic blood pressures and flows from structural anomalies adds further malformations such as chamber dilation or hypertrophy as well as abnormal blood vessel growth and formation.

Right-to-left shunting is present in patients who manifest cyanotic right-sided obstructive heart disease. Examples include deoxygenated blood passing to the left heart via a patent foramen ovale (PFO) or atrial septal defect (ASD) as might be found with severe Ebstein anomaly (EA) or a ventricular septal defect (VSD) in TOF. Those patients who do not present with neonatal cyanosis may manifest periodic cyanosis from variations in shunt direction, depending on the relative pressures between the right and left chambers of the heart. When right heart pressures are higher than left, the right-sided hypertension can be partially relieved by the right-to-left blood flow when septal defects are present. With severely restrictive septal defects, inadequate relief of right-sided hypertension manifests with CHF.

The degree of neonatal systemic hypoxemia that accompanies right-sided obstruction is also dependent on the patency

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of the ductus arteriosus. Pulmonary blood flow (PBF) in the presence of severe obstructions of the right heart, such as with critical pulmonary stenosis (PS) or pulmonary atresia (PA), might be entirely dependent on a patent ductus arteriosus (PDA). Affected neonates can rapidly show signs of increasing hypoxemia, such as respiratory distress and deepening cyanosis when the ductus arteriosus begins to close shortly after birth unless the ductal patency is stabilized with exogenous prostaglandin E_1 (PGE_1).

Congenital malformations that impede blood flow through the right heart can occur at a single critical anatomical area or a combination of areas. These include the right AV valve, the outflow tract of the right ventricle (RV), the pulmonary valve (PV), and the main pulmonary artery (MPA) and/or branch pulmonary arteries (BPAs). Commonly, congenital malformations affect several of these critical areas simultaneously, such as in TOF. Malformations can occur directly as a result of aberrant movement of tissues during development or indirectly as a result of impaired flow hemodynamics due to misaligned structural anatomy. Often the resultant congenital heart deformity is a combination of both processes.

The physiology of right-sided obstructive defects and the changes that occur with palliative or reparative intervention in the context of perioperative anesthetic care and planning for such patients are described in this chapter for:

- EA
- TOF
- PS with intact ventricular septum (PS/IVS)
- PA with intact ventricular septum (PA/IVS)
- PA and VSD with major aortopulmonary collateral arteries (MAPCAs).

Other right-sided obstructions such as those that result in a single functional ventricle (e.g. tricuspid atresia) are covered elsewhere in this book. See Chapter 30.

Ebstein anomaly

Incidence, anatomy, and natural history

Although EA occurs in only 0.3–0.7% of CHD, it is the most common congenital malformation of the tricuspid valve (TV) [1]. The incidence is approximately 1/10,000 live births [2]. EA was first described by Ebstein in 1866 [3] from necropsy findings. Clinical diagnosis was not achieved until 1949 [4] because the clinical presentation of more severe cases with diminished PBF and cyanosis resembled TOF, and partial competence of the malformed TV often was enough to prevent signs of CHF until late in evolution of the disease [5]. EA is characterized by a malformed TV and RV [6] (Table 28.1). With advent of cardiac catheterization and echocardiography, cardiologists were much more able to diagnose EA with certainty.

The highly varied range of dysplastic characteristics of EA causes extreme variations in clinical presentation from the neonate to the adult [7–9] (Figures 28.1–28.2, Table 28.1). The septal and posterior leaflets vary in the apical displacement of their attachments, and in approximately one third of cases the septal and/or posterior leaflets may remain adherent to the ventricular myocardium due to a failure of delamination. The anterior leaflet is attached at the functional annulus in a position superior to the other leaflets, but it is morphologically abnormal. Large with apparent redundant tissue, the leaflet frequently appears sail-shaped, often with fenestrations, and with abnormal RV attachments at the boundary of the inlet and trabecular areas. The anterior leaflet and/or the shortened chordae/dysplastic papillary muscles can restrict blood flow from the atrium/atrialized RV to the trabecular RV. Slits or perforations in the abnormally fixed anterior leaflet can be a significant obstruction. The shortened chordae extend from dysplastic papillary muscles. The trabecular RV is small, and sometimes very small, lacking an inlet chamber. Trabecular RV myocardial function can be normal or impaired with thin walls. An interatrial shunt is almost invariably present as over one third will have an ASD and most of the remainder will have a PFO.

Table 28.1 Characteristics of the malformed tricuspid valve and right ventricle in Ebstein anomaly

- The septal and posterior leaflets of the tricuspid valve fail to separate from the underlying myocardium
- The functional annulus of the tricuspid valve is displaced toward the apex; the septal leaflet is most displaced followed by lesser displacement of the posterior leaflet and least displacement of the anterior leaflet.
- The anterior leaflet is large with redundant tissue, often with fenestrations, and is tethered.
- A portion of the right ventricle located below the right coronary sulcus and above the functional but displaced annulus (the "atrialized" right ventricle) is dilated with an often thin and dysplastic freewall.
- There is dilation of the atrioventricular junction, the location of the true tricuspid valve annulus.

The line formed at the site of the distally displaced tricuspid leaflets serves as a functional TV ring and is the boundary between the trabecular and atrialized portions of the RV (Figure 28.3). Above this line of the distally displaced TV leaflets, the inlet portion of the anatomical RV serves as part of the RA. The atrialized portion of the RV is often thin and dilated with an abnormal ventricular electrical conduction pattern. Extreme thinning of the atrialized or inlet RV wall causes it to exhibit paradoxical movement with ventricular systole and dilation with RA contraction. The RA is dilated and sometimes massively dilated. The dilation of the atrialized RV creates an abnormal position for the interventricular septum, compromising left ventricular (LV) geometry and reducing the size of the LV chamber. There is increased fibrosis in both ventricles.

On prenatal ultrasound screening, the most severe forms of EA present with hydrops fetalis characterized by a massively enlarged heart and pulmonary hypoplasia. Lesser affected infants will have a neonatal course dependent on the severity of the EA defects, ranging from asymptomatic to cyanosis of varying degrees. Cyanotic neonates with severe obstruction will show signs of CHF that could lead to death. In general, cyanotic neonates with EA require intervention for survival. For lesser affected infants, the clinical presentation ranges from asymptomatic to progressive CHF depending on the degree of apical displacement of the TV. Diagnosis

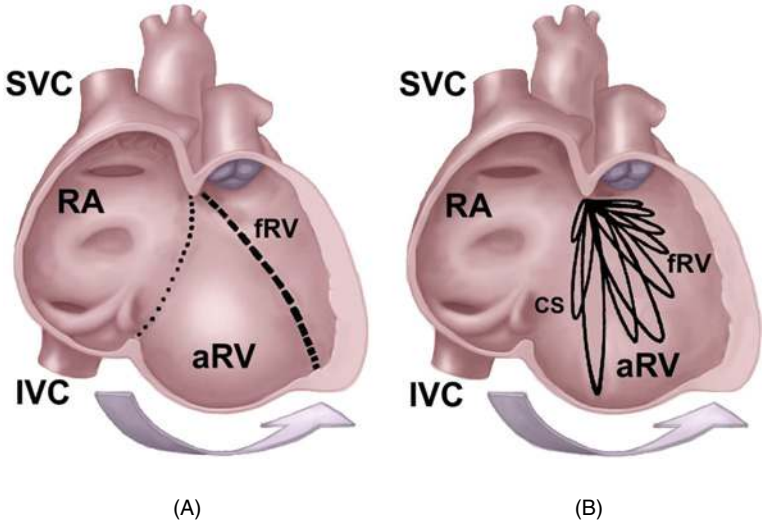


Figure 28.1 (A) Normal tricuspid valve attachments at the atrioventricular junction (dotted line) and the direction of the hinge line (dashed line) of the valve in Ebstein malformation. (B) The location of the functional orifice of the abnormal valve (black ovals) as observed in the series of hearts examined by Schreiber et al. [7]. aRV, atrialized right ventricle; CS, coronary sinus; fRV, functional right ventricle; IVC, inferior vena cava; RA, right atrium; SVC, superior vena cava. (Source: Dearani et al. [8]. Reproduced with permission of Cambridge University Press.)

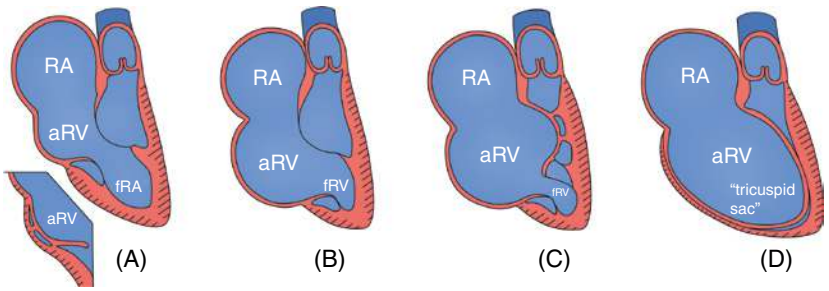


Figure 28.2 Carpentier classifications of four anatomical types of Ebstein anomaly. (A) Small, contractile, atrialized chamber (the "atrialized right ventricle, aRV") with mobile anterior leaflet with no or limited (inset drawing) obliteration of the interchordal space and moderate apical displacement of septal and posterior leaflets. (B) Large, noncontractile atrialized chamber with no or limited interchordal space obliteration and mobile anterior leaflet with marked apical displacement of septal and posterior leaflets. (C) Anterior leaflet with restricted motion due to obliteration of interchordal spaces and attachment of the inferior edge to the ventricle and fibrous bands attaching other leaflet areas to the infundibulum, marked displacement of septal and posterior leaflets that may be severely hypoplastic. Atrialized chamber is large with a thin, noncontractile wall. (D) Leaflet tissue forms a continuous sac adherent to the dilated right ventricle, creating a "tricuspid sac," with obliterated interchordal spaces. RA: right atrium; RV: right ventricle. (Source: Carpentier et al. [9]. Reproduced with permission of Elsevier.)

is sometimes delayed until symptoms present in older children or young adults, and less commonly in middle age or later. Generally, exercise tolerance is minimally impaired in the mildly affected unless the foramen ovale is not patent. Adults who present with CHF from long-term effects of tricuspid regurgitation (TR) have a poor prognosis without definitive intervention. Severity cyanosis in children and young adults with EA is associated with a poor prognosis. Even milder forms of EA that present in late childhood, adolescence, or young adulthood often result in death from CHF in the second and third decades of life without surgical intervention. For those asymptomatic individuals who have not developed CHF, up to 20% may die of atrial and ventricular arrhythmias, sometimes as a sudden death. Paradoxical emboli, abscess formation, and less commonly endocarditis contribute to later fatalities [10].

Pathophysiology

The TR of EA and the degree of downward displacement of the TV variably impair adequate development of the heart. Diminished flow through the RV *in utero* may play a role in the development of right ventricular outflow tract obstruction (RVOTO), PS, and even PA. Significant TR places a volume load on the RV that results in a largely dilated RV that impairs LV function. Severe TR produces a massively ballooned RA. As pulmonary vascular resistance (PVR) decreases and stabilizes to near adult values, forward flow in the neonatal right heart can cause EA signs to improve [11, 12]. A cyanotic neonate with an unrestrictive ASD may eventually become acyanotic with acceptable cardiac output (CO). However, an infant with a restrictive ASD can have a low CO due to LV impairment from malposition of the interventricular septum with paradoxical motion.

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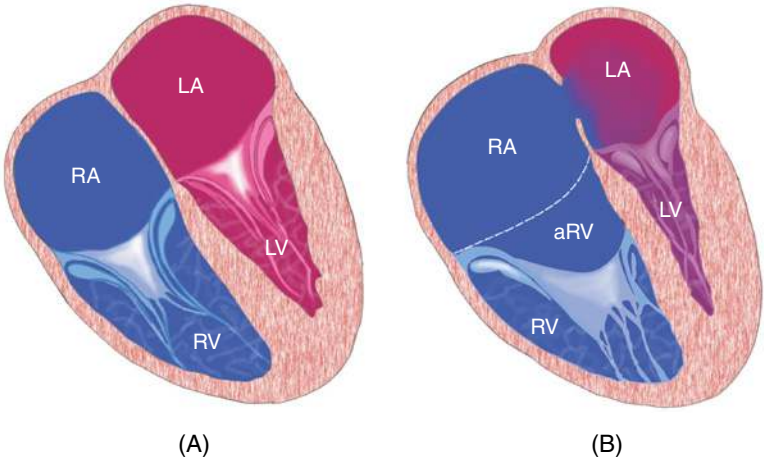


Figure 28.3 (A) Normal heart, and (B) heart with Ebstein anomaly. Carpentier class A (dashed white line indicates level of atrioventricular junction). aRV, atrialized right ventricle; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Source: Michael L. Schmitz, MD.)

The distortion of atrial and ventricular chambers with EA is associated with arrhythmias that can further impair function and be life-threatening. As many as 25–30% of individuals will have atrial flutter, atrial fibrillation and paroxysmal supraventricular tachycardia. Other electrophysiological abnormalities are also frequently present [1] (Table 28.2).

Familial genetically inherited forms of EA are sometimes associated with LV noncompaction cardiomyopathy. In fact, the type of CHD most associated with this myopathy is EA. This combination is associated with mutations in the B-myosin heavy chain gene MYH7. Although autosomal dominant, gene penetrance is variable as some individuals do not have cardiac abnormalities [13]. Characteristics of LV noncompaction include prominent trabeculations with deep intratrabecular recesses that give the LV a spongy appearance on cardiac ultrasonography. Added risks of CHF, arrhythmias, thromboemboli, and sudden cardiac death occur with this combination [14]. Recent genetic analyses of patients with EA suggest multiple genetic associations with genes involved with myocardial development or function other than MYH7 including NKX2-5, TTN, MYH6 as well as a number of various single nucleotide alterations, genetic locus deletions/duplications and copy number variants [15] not infrequently associated with cardiomyopathies.

Table 28.2 Major electrophysiologic abnormalities in Ebstein anomaly

- Intra-atrial conduction disturbance: right atrial P-wave abnormalities, PR prolongation
- Atrioventricular nodal conduction: PR interval prolongation
- Infranodal conduction
  - Intra-His or infra-His conduction abnormalities
  - Right bundle branch block
  - Bizarre *second* QRS attached to preceding normal QRS
- Type B Wolff–Parkinson–White pre-excitation
- Supraventricular tachycardia
- Atrial fibrillation or flutter
- Arrhythmogenic atrialized right ventricle
- Deep Q waves in Leads V_{1-4} and in inferior leads

Progressive right heart failure resulting from TR, an inadequately sized RV pumping chamber, and other right-sided obstruction combined with the EA TV are sometimes indications for surgery in the infant or child. Otherwise, moderate CHF can be treated with diuretic therapy, perhaps combined with digoxin. Medical therapy and perhaps catheter ablation can be used to control some types of arrhythmias. However, if deterioration of the TV and RV appears progressive, long-term outcome will be improved with earlier surgical intervention [16].

Surgical and transcatheter approaches and outcomes

The timing of intervention for EA is determined by the degree of apical displacement of the functional TV, the competency of the TV, the presence of PA or circular shunting, and the age of the patient (Figure 28.4). Depending on the size of the trabecular RV, patients may undergo two ventricle repair or be palliated with one-and-one-half (1.5) or single ventricle surgical pathways. Timing of intervention in neonates also takes into account potential RVOTO and allowance for PVR to resolve to near adult pressures. Only the most severely compromised infants are generally considered for cardiac transplantation [11] such as those with poor biventricular function and/or uncontrollable arrhythmias. Decision-making for the type of surgical repair or palliation depends first on the age of the patient and secondly on two key elements: the TV morphology and the size of the trabeculated RV (Figure 28.5). A number of infants with adequate trabecular RVs have successfully undergone two ventricular repairs.

In 1958 after studying EA heart specimens, Hunter and Lillehei [17] suggested a potential repair for the TV but advances in valvuloplasty ultimately led to the first successful EA TV repair in 1963 [18]. From 1972 onward, further refinements in valvuloplasty by Danielson et al. [19] and others have improved survival for patients with EA (Table 28.3).

Techniques for valvuloplasty of the EA TV have evolved for nearly 60 years. A technique introduced in 1972 altered the anterior leaflet of the TV such that it would approximate

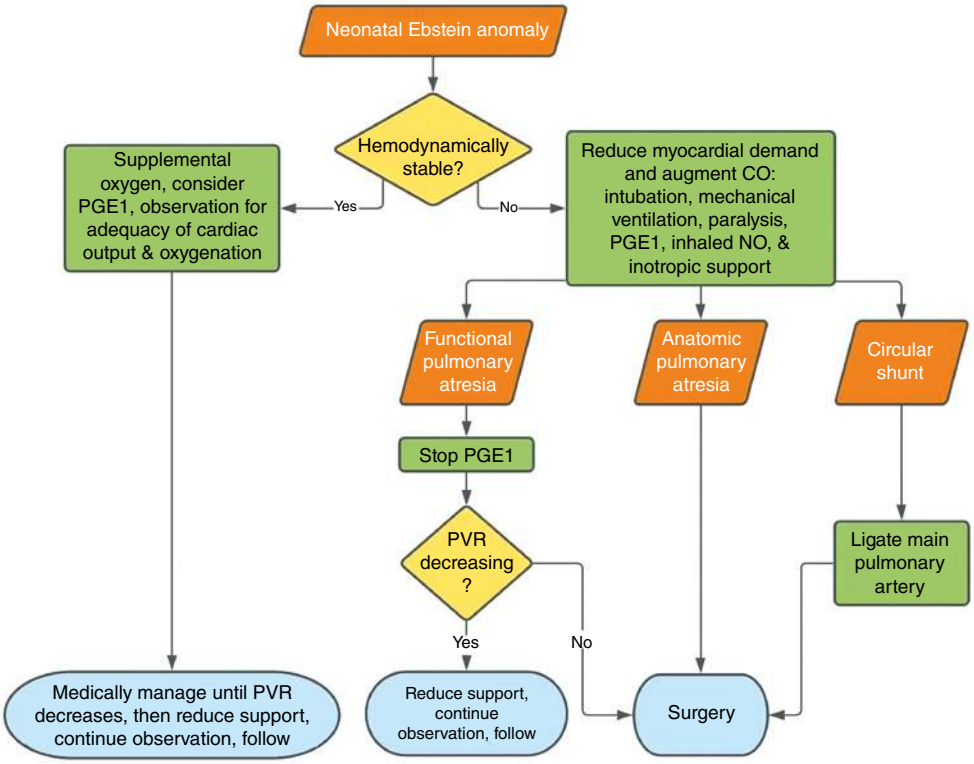


Figure 28.4 Algorithm for treatment of neonatal Ebstein anomaly. CO, cardiac output; NO, nitric oxide; PGE1, prostaglandin E_1; PVR, pulmonary vascular resistance. (Source: Michael L. Schmitz, MD.)

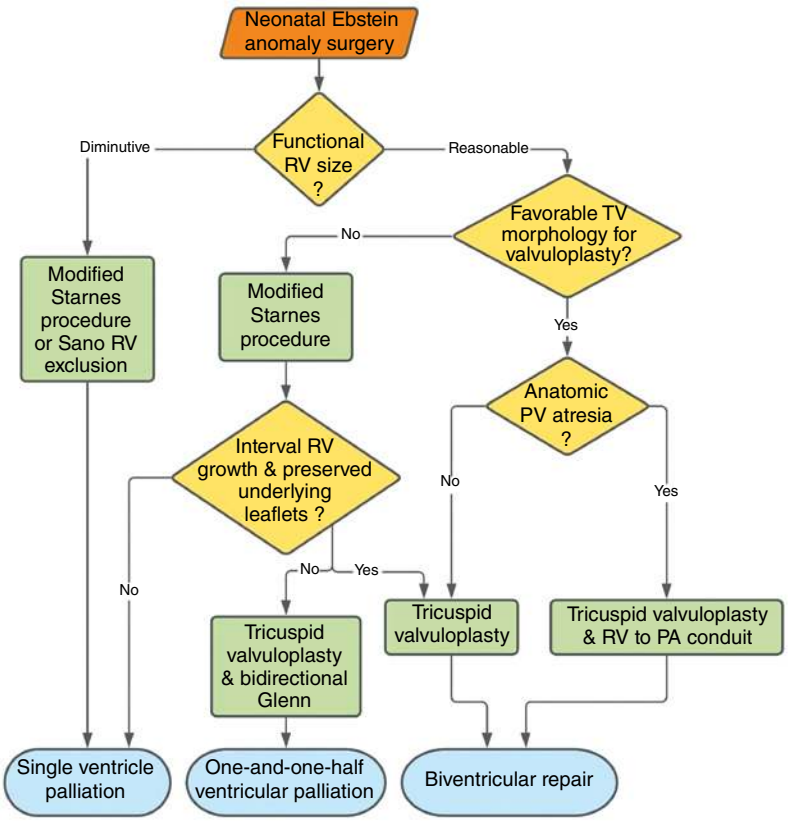


Figure 28.5 Algorithm for neonatal Ebstein anomaly surgical intervention. PA, pulmonary artery; PV, pulmonary valve; RV, right ventricle; TV, tricuspid valve. (Source: Michael L. Schmitz, MD.)

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Table 28.3 Developments in the treatment of Ebstein anomaly

- Valvuloplasty techniques
  - Improved TV coaptation, decreasing TR
  - Relocation of the TV to the true, and often remodeled annulus
  - Centralized flow in the remodeled TV with less impedance
  - Delamination of valve tissue attached to RV wall or septum
  - Use of the cone technique for those valves with suitable TV tissue
  - Stabilization of the true TV annulus with rings and partial rings
- Improvements in functional RV morphology by employing plication techniques to the atrialized RV
- Advances in electrophysiological ablation technology with improved success in ablating accessory conduction pathways

the ventricular septum or the small, malformed septal leaflet during systole. Coaptation of the TV was facilitated by plicating the TV annulus at the apical boundary of the atrialized RV to reduce annulus diameter [19]. Further modifications for mobilizing and fixing the anterior and posterior leaflets at the true tricuspid annulus while utilizing a valve ring ensued [9]. Some infants with adequately sized RVs have done well with an aggressive two-ventricle repair that included reconstruction of a monocuspid TV from the anterior leaflet with or without translocation of the leaflets to the true annulus, ventriculorrhaphy, reduction atrioplasty, subtotal closure of the ASD, and repair of other associated defects [20]. Others have focused on a bicuspid TV repair without repositioning the valve to the true annulus [21].

Building on a previous technique, da Silva et al. [22] developed a method known as the cone reconstruction that enhances available valve tissue by surgically delaminating leaflets attached to the RV wall and septum. The cone reconstruction of the TV for EA began to be developed in 1989 and has evolved to become a successful option for patients with adequate available valvar tissue and trabecular RV chambers. The TV leaflets are mobilized and reattached to the true TV annulus. The anterior and posterior leaflets are sutured together into a cone shape, incorporating the septal leaflet into the cone when possible. The atrialized RV is longitudinally plicated. Flexible annuloplasty rings (partial rings for children to allow for growth) are sometimes used to add stability to the dilated TV annulus [23] (Figure 28.6). Although cone reconstruction has been successful

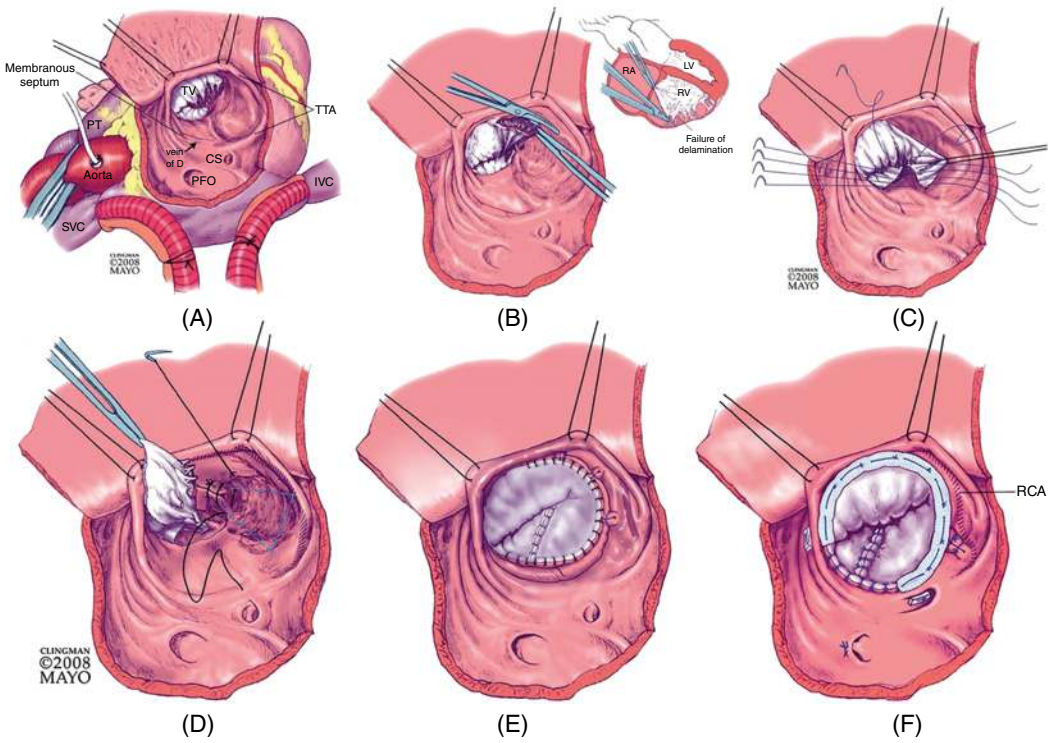


Figure 28.6 Key components of the cone repair. (A) Standard aortic and bicaval cannulation. Right atriotomy is parallel to the atrioventricular (AV) groove. Anatomic examination of the tricuspid valve (TV) and the atrialized right ventricle (RV). Membranous septum and AV node are marked by small vein (vein of D). (B) Delamination of the TV. First incision is made at 12 o'clock in the anterior leaflet a few millimetres away from the true annulus. Surgical delamination is the division of the fibrous and muscular attachments between the body of the leaflet(s) and the free wall of the RV. Delamination must continue to all attachments between the AV groove and the leading edge of the leaflets (close to the RV apex) while keeping the attachments at the leading edge of the leaflet intact. (C) Rotation of leaflet tissue. Following mobilization of all leaflet tissue, the inferior leaflet, or most medial aspect of the anterior leaflet, is rotated clockwise to meet the mobilized septal leaflet. These leaflets are approximated with suture. At completion, the neo-TV orifice should be composed of 360° of leaflet tissue. Prior to reattachment, the atrialized RV is examined to determine need for RV plication. (D) RV plication. Internal triangular plication of portions of the atrialized RV reduces tension on the repair, reduces size of the TV annulus, and eliminates noncontractile RV. Plication is started close to the RV apex and proceeds to the AV groove. Care must be taken to avoid injury to the right coronary artery. (E) Attachment of neo-TV to the true annulus. The septal leaflet is reattached to the ventricular septum (just caudal/ventricular side of the true annulus). (F) Repair can be reinforced with either a felt band (in younger children) or an annuloplasty band (older children and adults). CS, coronary sinus; IVC, inferior vena cava; LV, left ventricle; PFO, patent foramen ovale; RA, right atrium; RCA, right coronary artery; SVC, superior vena cava; TTA, true tricuspid annulus. Copyright © Mayo Foundation for Medical Education and Research. (Source: Holst et al. [23]. Reproduced with permission of Mayo Foundation for Medical Education and Research.)

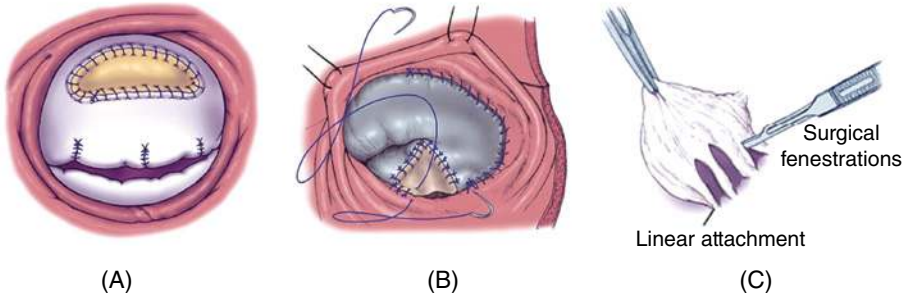


Figure 28.7 Tricuspid valve (TV) leaflet augmentations for the cone repair. Leaflet augmentation can be accomplished with either autologous pericardium or CorMatrix membrane to increase the height of the anterior TV leaflet (A) or to increase the TV diameter at the annulus (B). When there is a linear attachment of the leading edge of the anterior TV leaflet to the right ventricular endocardium, autologous neochordae can be fabricated with surgical fenestrations (C). (Source: Dearani et al. [29]. Reproduced with permission of Elsevier.)

in neonates [24, 25] and small infants [26], valve rings are not an option for these small patients. When tissue is found to be insufficient, leaflets can be augmented with patch material [27, 28] (Figure 28.7). The cone operation improves coaptation of the TV leaflets and allows for centralized flow.

Utilization of a semi-functional RV by combining RV output to the MPA from the inferior vena cava (IVC) with a bidirectional Glenn (BDG) anastomosis in a 1.5 ventricular repair can be beneficial. Compared to patients converted to single ventricle physiology, 1.5 ventricular pulsatile flow to the pulmonary arterial tree might reduce MAPCA development while inclusion of hepatic venous flow to the pulmonary arterial tree might reduce formation of pulmonary arteriovenous malformations. Even a hypoplastic RV may increase CO with increased cardiac demand beyond what could occur with a Fontan circulation. The BDG can be used to reduce RV preload to hypoplastic EA RVs or those with moderate degrees of TV stenosis, allowing for closure of a coexisting ASD or PFO.

In some cases of severe EA, there may be no identifiable TV leaflet tissue available for reconstruction. In the absence of available leaflet tissue combined with a severely dilated dysfunctional RV and secondary LV compression, a fenestrated RV exclusion procedure with a systemic-to-pulmonary arterial shunt may be the best option for an infant [30]. The modified Starnes procedure is accomplished by placing a patch with a 5 mm fenestration at the level of the true tricuspid annulus while allowing the coronary sinus to remain on the RA side of the patch. The fenestration allows for thebesian venous drainage from the excluded RV to the RA. If there is pulmonary arterial insufficiency, the RV to pulmonary connection is interrupted. As with all single ventricle palliations, an unrestricted atrial communication is ensured. Later, the infant or child may advance to a BDG or Fontan palliation. A limited follow-up for 12 patients has shown that the RV involutes sufficiently to allow improved geometry and function of the single LV [31]. The Sano RV exclusion technique [32] for EA is similar but employs an RV to pulmonary artery conduit rather than a systemic-to-pulmonary shunt to provide PBF. The advantage of the modified Starnes procedure over the Sano RV exclusion technique is that the already reduced functional RV myocardium is less compromised without the ventriculotomy required for the RV to pulmonary artery conduit.

Complications of the cone procedure are similar to other TV repairs for EA. Inadvertent tricuspid stenosis or suture dehiscence are possible. Sutures too near the AV node can cause third-degree heart block. Distortion caused by plication of the atrialized RV and TV annulus can impair right coronary artery blood flow. Outcomes are compromised when neonatal EA is associated with RVOTO, PA, small pulmonary arteries, or any congenital disease that causes LV dysfunction.

Rhythm disturbances can occur at any time with EA. Temporary pacing wires should be placed on the RA and RV near the conclusion of surgery as postoperative pacing could be necessary. Generally, teenaged and adult patients who do not require postoperative pacemakers have fewer rhythm disturbances on follow up [33]. Wolff-Parkinson-white accessory pathways, often near the orifice of the TV, are present in 10–20% of EA.

Outcome studies are limited for the cone reconstruction. A follow-up of 52 patients ranging in age from 0.25 to 49 years (mean 18.5 ± 13.8 years) showed that the cone repair maintained its integrity and there was an increase in RV function relative to body surface area indexing. Two of the 52 died postoperatively in-hospital and one was lost to follow up resulting in a statistical survival of 86.2 ± 8%f at 7 years. Of the followed 49, four underwent TV revision (3, 4, 5, and 10 years postoperatively), one received a pacemaker for intermittent episodes of complete AV block 1 year after surgery, three had atrial arrhythmias (one successfully ablated and the other two medically controlled). Eleven had Wolff-Parkinson-White syndrome and had the anomalous bundle surgically sectioned; ten were successful and one had repeated ablations, developed TR, and then underwent TV revision 5 years postoperatively [34].

A single institution review of 151 EA patients with a mean age of 28 years (56 patients less than 18 years of age) who underwent either cone reconstruction (n = 38, age 31 ± 19 years), conventional repairs (n = 94, age 26 ± 18 years), or TV replacement (n = 19, age 36 ± 21 years) presented mid-term follow up comparisons for cone repair, conventional repairs, and TV replacement. Cardiopulmonary bypass (CPB) times as well as aortic cross clamp times were longer for cone repairs than either conventional repairs or TV replacement. Cone repair was more successful than conventional repairs at mid-term follow up (8 years) with moderate or less TR (p = 0.031) and a reduced incidence of post-repair severe TR that did not reach clinical significance. Of note, most of the cone repairs were performed more recently than many of the conventional repairs [35].

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In the largest series to date from the Mayo Clinic [28], 235 consecutive cone repairs for patients with EA and a median age of 15 years (range 6 months to 73 years) showed only one early death of a 50-year-old from low CO syndrome related to endocarditis from pacemaker leads. Extracorporeal membrane oxygenation (ECMO) was needed for the one adult early mortality patient and for 5 pediatric patients with severe preoperative RV dysfunction and dilation. Cone repair was the primary correction in 80% and a re-repair in 12%. Early reoperation for recurrent TR occurred in 5.9% (7 children and 7 adults). TV replacement was ultimately required for 6/7 adults, but 6/7 children had a successful reoperation. Of those requiring reoperation, 11 of the 14 were in the first third of the series, suggesting a learning curve for a successful cone repair. Supplemental techniques were used in many, including the BDG anastomosis in approximately 20% (41 children and 5 adults), annuloplasty bands, leaflet augmentation, and use of neochordae.

In general, TV replacement is reserved for irreparable TV and RV anatomy as reoperation and repeat cardiotomy for TV replacements will likely be necessary for the patient's lifetime. In addition, options for prosthetic valves are limited or non-available for small infants and children. Some teenaged or adult patients with late diagnoses might have incurred TV leaflet damage from turbulent blood flow or endocarditis that preclude successful repair, and TV replacement may be the best option. For select patients such as the elderly, TV replacement might be considered if advantages of lessened CPB time outweigh the longer time needed for TV repair. Bioprosthetic valves are preferable in the tricuspid position due to their lower thrombogenicity over mechanical valves. When placing the prosthetic TV, care is exercised in avoiding the conduction system on the septal side and the right coronary artery on the anterior and inferior sides of the implanted TV as well as avoiding the right ventricular outflow tract (RVOT) and impingement of the valve struts on the AV node. Similar considerations will apply to future development of percutaneous TV replacement.

Older children and adults with preoperative paroxysmal atrial fibrillation or atrial flutter might be candidates for a modified right-sided maze procedure or cavotricuspid isthmus ablation using either radiofrequency or cryoablation [23] (Figure 28.8). Those with continuous atrial fibrillation may do better with a biatrial maze [36].

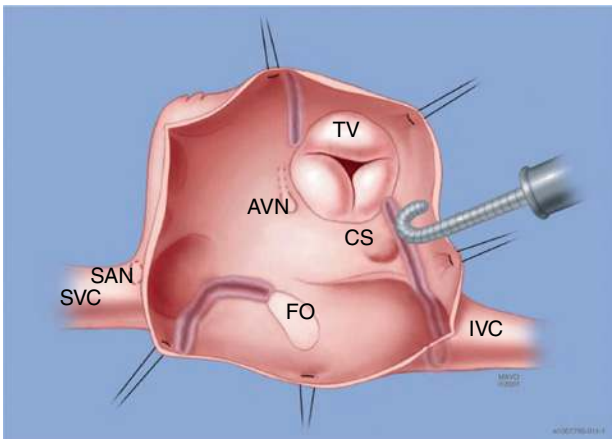


Figure 28.8 Cryoablation for atrial flutter/fibrillation in Ebstein anomaly. AVN, atrioventricular node; CS, coronary sinus; FO, foramen ovale; IVC, inferior vena cava; SAN, sinoatrial node; SVC, superior vena cava; TV, tricuspid valve. Copyright © Mayo Foundation for Medical Education and Research. (Source: Holst et al. [23]. Reproduced with permission of Mayo Foundation for Medical Education and Research.)

Anesthetic considerations

Preoperative

For neonatal presentation of EA, signs of right heart failure and systemic hypoxemia are most critical. Dyspnea, cyanosis, and hepatomegaly suggest that the infant should be supported such that demands on CO and oxygen consumption are minimized. The most severely affected infants benefit from intubation, mechanical ventilation, paralysis, and sedation to reduce work of breathing and demands on CO. Oxygen, inhaled nitric oxide (iNO, if pulmonary hypertension is suspected), inotropic support, and possibly PGE_1 may increase oxygen delivery. For the less affected infant, signs of fatigue with feeding, feeding intolerance, irritability, diaphoresis, dyspnea, and episodic cyanosis with distress suggest a poorly functioning heart. Oxygen, milrinone, and possible PGE_1 may be beneficial prior to anesthesia. Some neonates will manifest a gradual improvement in right heart forward flow and a reduction in right-to-left shunting and cyanosis as TR declines. Neonatal surgical intervention, when possible, is delayed until PVR has declined significantly.

For the toddler, older child, adolescent, or even young adult, functional symptoms of dyspnea with exertion, excessive fatigue with daily activities or as compared to peers, and certainly signs of cyanosis as well as the trends in symptomatology in recent months give some insight into the severity of EA. In the older child and young adult, syncope, chest pain, and palpitations should be investigated for the presence of arrhythmias.

Physical examination often reveals a soft, high-pitched systolic murmur, sometimes accompanied by triple or even quadruple heart sounds. A mid-diastolic murmur is sometimes found at the left sternal border and apical areas and has a soft, scratchy sound. A persistently split-second heart sound due to delayed emptying of the RV is usually present and varies little with respiration. Pediatric patients with myocardial failure are diaphoretic, tachypneic, and irritable. Chest auscultation can be notable for rales if LV function is impaired by a dilated RV. Abdominal examination often reveals hepatomegaly on palpation. Moderate to severe cardiomegaly is found on the chest radiograph, and pulmonary vascularity is reduced. The silhouette of the heart is globular due to the enlarged RA. In fact, the electrocardiogram (ECG) usually shows an increased duration for the P-wave suggesting right atrial enlargement, an increased PR interval, and not unusually a complete or incomplete right bundle branch block. In at least 10–15% of patients, the pre-excitation patterns of Wolff-Parkinson-White syndrome are present. An echocardiogram is usually diagnostic for EA, showing a large TV orifice with apical displacement of the septal leaflet [29] (Figure 28.9). Cardiac catheterization is seldom useful, even for the most commonly associated defects, and place the patient at risk for development of tachyarrhythmias. Magnetic resonance imaging (MRI) can be valuable in estimation of the size of the functional RV and accurately

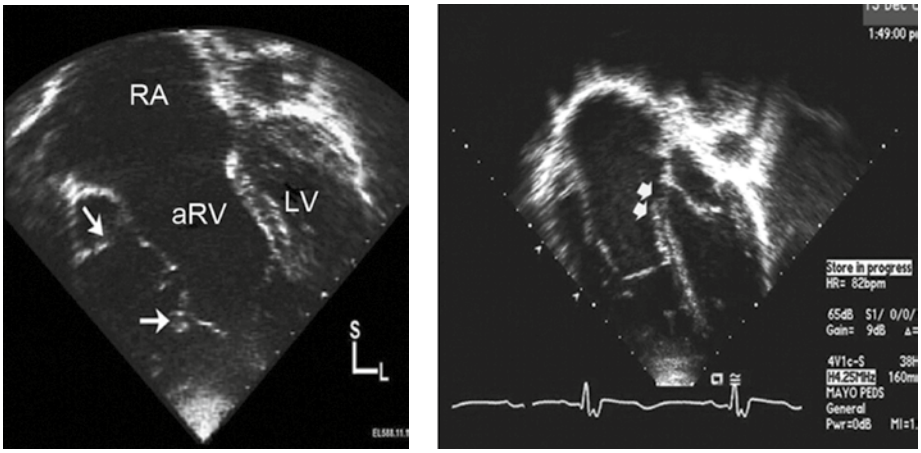


Figure 28.9 Preoperative four-chamber view echocardiogram evaluation for potential cone repair. (A) Multiple attachments between the anterior leaflet and the RV free wall from base to apex (arrows). (B) The undelaminated septal leaflet (arrows) suggests that this leaflet tissue can be recovered increasing the chances for a successful repair. aRV, atrialized right ventricle; LV, left ventricle; RA, right atrium. (Source: Dearani et al. [29]. Reproduced with permission of Elsevier.)

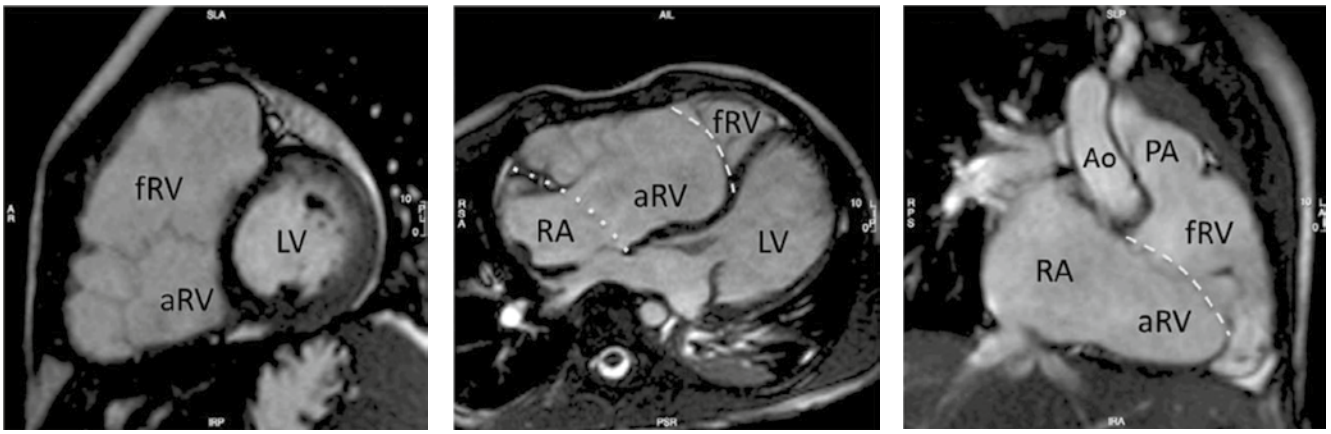


Figure 28.10 Cardiac magnetic resonance imaging of Ebstein anomaly. (A) Short-axis plan at mid-ventricular level. (B) Four-chamber view. (C) Right ventricular inflow-outflow view. The atrioventricular junction (dotted line) and the functional tricuspid valve orifice (dashed line) define the basal and apical boundaries (respectively) of the atrialized right ventricle (aRV). The functional right ventricle (fRV) lies between the dashed line and the pulmonary valve. The anatomic RV includes both the aRV and fRV. The tricuspid valve functional orifice is rotated apically and superiorly towards the RV outflow tract. Ao, aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium. (Source: Holst et al. [23]. Reproduced with permission of Mayo Foundation for Medical Education and Research.)

measuring the displacement of the TV leaflets (Figure 28.10). Though both MRI and echocardiography are useful in detecting associated defects, echocardiography may underestimate the degree of TR but is more effective in detecting small shunts from associated defects than MRI [37].

Hypoxemic neonates should be managed with interventions aimed to decrease and avoid increasing PVR. For the mechanically ventilated neonate, adequate tidal volumes and minute ventilation must be achieved with minimum airway pressures. Those infants with marginal heart function may benefit from iNO by reducing PVR and enhancing right heart to pulmonary artery flow. In addition, functional and anatomical obstructive components to PBF may be further defined by the addition of iNO as poor right heart function is anticipated to improve with iNO while anatomical obstructions in the RVOT, PV, and PAs will remain. In the first couple weeks after birth, pulmonary arterial blood flow may require augmentation with a PDA maintained with PGE_1. However, too much flow through a large PDA can result in cardiac failure and loss of systemic and pulmonary perfusion with a phenomenon known as "circular shunt" [38] (Figure 28.11). Circular shunt results when generous flow to the pulmonary arterial system from the aorta via the PDA follows a retrograde path of least resistance when the PV and TV are incompetent and there is an interatrial communication. Sequentially, flow proceeds from the PDA, BPA, MPA, PV, RV, RA, ASD or PFO, LA, LV, and finally the aorta. Perfusion of the pulmonary capillary bed is diminished and

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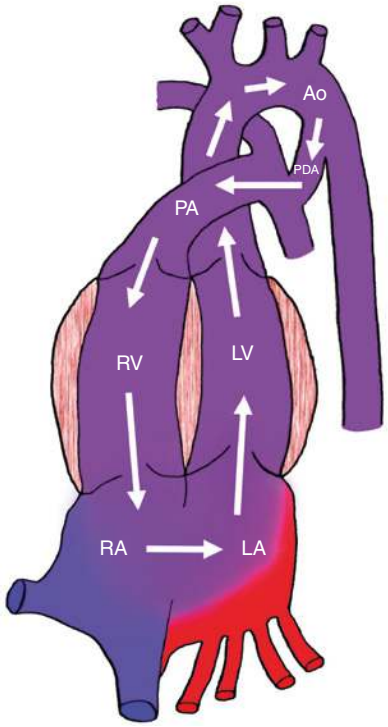


Figure 28.11 Circular shunt: aortic blood enters the lower pressure pulmonary artery (PA) via the patent ductus arteriosus (PDA). Pulmonary insufficiency allows blood to continue retrograde into the right ventricle (RV), right atrium (RA), left atrium (LA), left ventricle (LV), and then again to the aorta (Ao). (Source: Schmitz et al. [38]. Reproduced with permission of John Wiley & Sons.)

CO to the vital organs is reduced. PGE_1 should be discontinued so that the PDA becomes smaller and more resistant to flow, reducing the circular shunt and high output failure [12].

Most neonates and young infants may not require anxiolytic premedication. Older infants, those who have developed stranger anxiety (approximately 9 months of age), and children often benefit from anxiolytic administration of midazolam. Midazolam may be given orally (0.5–0.75 mg/kg up to 15–20 mg) or intravenously (IV) (0.1–0.15 mg/kg up to 2–4 mg). Anxiolysis can be helpful in reducing or avoiding decreases in PBF that can result with crying or breath-holding during application of the mask anesthetic. In some cases, a sleeping child who has received dexmedetomidine can be safely transported and undergo a safe anesthetic induction, but this technique requires planning. Loading with 0.5 to 1.0 μg/kg IV over 10 minutes is often sufficient but requires monitored attention for potential bradycardia. For patients who do not yet have IV access and are to undergo a mask anesthetic induction or merely have a non-stimulating procedure (such as a sedated transthoracic echocardiogram), intranasal dexmedetomidine is administered with a nasal atomizer (2–3 μg/kg, 100 μg/mL) often results in adequate sedation. The time required for mean onset of sufficient sedation is 10–24 minutes for 3 μg/kg [39]. Reducing ambient light and background noise while ensuring that the child is warm and comfortable facilitates the sedative effect. Relative contraindications for dexmedetomidine include poor CO, hypovolemia, bradycardia or risk for bradycardia, AV nodal block, or medications that delay AV conduction or increase vagal tone [40].

Intraoperative

An inhalational induction with nitrous oxide and sevoflurane is appropriate for infants and children with mild to moderate EA. Inhalational induction is slowed by interatrial left-to-right shunting as well as by decreased CO. Ketamine (1–4 mg/kg) or propofol (1–2 mg/kg) are IV induction alternatives for mild to moderate disease. For those with severe EA, hemodynamic stability is maintained in a euvolemic patient in most instances with IV ketamine (1–4 mg/kg) or etomidate (0.2–0.3 mg/kg) without inducing detrimental myocardial depression or afterload reduction.

Sufficient right heart preload must be maintained to maximize the EA right heart forward flow. As the anesthetic progresses, increases in vascular compliance are accommodated with replacement of intravascular volume, such as 5% albumin, crystalloid solutions, or in the anemic patient, packed red blood cells (PRBC). Muscle relaxants are selected based on the anticipated duration of the procedure and the occasional need for a modified rapid-sequence induction. Rocuronium offers quick action for induction and intubation (0.6–1.2 mg/kg) as well as subsequent maintenance of muscle relaxation (0.1–0.2 mg/kg every 20–30 minutes). Pancuronium is another option with a longer duration of action (0.06–0.1 mg/kg for induction and approximately 0.01–0.02 mg/kg for redosing). Both muscle relaxants induce ganglionic blockade and vagolysis, effecting a higher baseline heart rate. For CPB cases, opioid-based anesthetics combined with modest levels of potent inhalation agents such as sevoflurane or isoflurane are common. The relative balance of opioids and inhalation anesthetic is based on the patient's ability to tolerate the myocardial depressant effects of higher ranges of inhaled halogenated agents and the plan for early versus delayed liberation from mechanical ventilation. For patients that will remain intubated with mechanical ventilation after arrival to the intensive care unit (ICU), fentanyl 10–15 μg/kg and 0.5–1.0 minimum alveolar concentrations (MAC) of halogenated agent may be used prior to CPB with a total fentanyl of perhaps 20–30 μg/kg combined with a morphine infusion of 30–35 μg/kg/hour started at the time of incision. If extubation in the operating room is anticipated, total fentanyl administration is approximately 10–20 μg/kg and halogenated agents are utilized at higher MAC as tolerated. A morphine infusion of 25 μg/kg/hour is started by the time of incision. For infants beyond the neonatal period, sedation with dexmedetomidine at 0.5 μg/kg/hour is added for sedation management in the postoperative period whether extubated in the operating room or later in the ICU. Plasmin–binding inhibitor antifibrinolytic drugs such as epsilon-aminocaproic acid or tranexamic acid infused during surgery and in the immediate postoperative period can reduce overall blood loss.

Monitoring for rhythm changes, especially tachyarrhythmias in EA, can be accomplished with a five-lead ECG and monitoring capable of displaying multiple tracings to facilitate identification of the arrhythmia. ST monitoring is helpful in identifying EA post-repair right coronary artery compromise which may be identified by ST elevation in leads II, III,

or AVF or reciprocal depression in I or AVL. Sometimes, temporary AV pacing may be necessary when complete heart block, junctional rhythms, or sinus node dysfunction present after removal of the aortic cross clamp in order to achieve hemodynamic function sufficient to separate from CPB. Depending upon the etiology of the rhythm disturbance, temporary pacing could be needed for a brief period after cessation of CPB, several hours, several days, or until a permanent pacemaker is placed. Other useful monitoring includes near-infrared spectroscopy (NIRS) for monitoring brain and somatic oxygenation, especially during the nonpulsatile flow of CPB. Near the end of CPB, intraoperative transesophageal echocardiography (TEE) is used to assess clearance of air bubbles in the systemic heart chambers, reconstructed TV function, ventricular contractility, and residual shunts in the immediate post-CPB period. Transcranial Doppler (TCD) flow velocity is not commonly utilized due to the technical difficulty in maintaining its positioning on the patient, but it has the ability to follow changes in cerebral blood flow velocities in unilateral or bilateral anterior and/or middle cerebral arteries during surgery. The TCD can also be used to detect gaseous or particulate emboli that enter the cerebral circulation.

Patients with good biventricular function and mild TR can be candidates for immediate extubation at the end of surgery provided that the rhythm is normal sinus or stable in a paced mode and there are no concerns for postoperative surgical bleeding. Inhaled halogenated anesthetics are utilized primarily after CPB, and muscle relaxant and opioids employed sparingly. After the sternum is closed, reversal of muscle relaxation and initiation of pressure-supported ventilation can begin. Adjunctive IV acetaminophen can be used to decrease opioid requirements at the end of surgery. Additional opioids can be titrated to the respiratory rate as surgical stimulation decreases and inhaled halogenated agents are weaned. Local analgesia administered by the surgery team decreases narcotic requirements at the end of the case. Dexmedetomidine sedation (0.3–0.5 μg/kg/hour) and morphine infusion (25 μg/kg/hour for extubated patients and 30–35 μg/kg/hour for mechanically ventilated patients) are continued upon transfer of the extubated patient to the ICU.

High risk patients, such as those who presented with severely dilated right hearts and compressed LVs, are not candidates for extubation in the OR. In addition to higher needs for inotropic support, such patients are at high risk for lethal ventricular arrhythmias in the post-repair period, especially if they have undergone RV plication. Antiarrhythmic medications such as lidocaine and amiodarone need to remain readily available. Patients who manifest runs of ventricular tachycardia or other ventricular arrhythmias should be placed on amiodarone (3–5 mg/kg over 30 minutes, then 2 mg/kg/day, maximum 20 mg/kg/day or 2.1 g/day) or lidocaine (20–50 μg/kg/min) infusions in the early postoperative period. Prophylactic amiodarone infusions may be considered for patients who present with severe right heart cardiomegaly. Right heart forward flow can be augmented with infusions of milrinone (0.2–0.5 μg/kg/min) and low-dose epinephrine 0.02–0.04 μg/kg/min. Preload to the right heart must be fastidiously maintained for a poorly functioning RV. In cases with elevated pulmonary vascular resistance, iNO can be instituted. Leaving the sternum open in highest risk patients facilitates access for ECMO in the case of cardiovascular collapse due to arrythmias, low cardiac output, or pulmonary hypertension.

Postoperative

In the ICU, continuous monitoring of the heart rhythm and arterial blood pressure is essential. Intravascular volume expansion options need to be readily available. Often, there may be post-CPB papillary muscle dysfunction, possibly of ischemic etiology. Early ICU echocardiography can show poor coaptation of the TV leaflets, but as the papillary muscle bundle dysfunction resolves, later echocardiographic examinations can show improving TV leaflet coaptation.

Pain is controlled with morphine infusions of 25–30 μg/kg/hour for extubated opioid-naïve patients and 30–40 μg/kg/hour for mechanically ventilated opioid-naïve patients. Dexmedetomidine 0.3–0.5 μg/kg/hour is used for sedation rather than relying on narcotic infusions for sedation. For the patients with poorly functioning RVs, gradual recovery from sedation is appropriate to allow for recovery of myocardial function prior to increased CO demands of the fully awake patient. Morphine boluses (20 μg/kg) can be added for breakthrough pain, and dexmedetomidine boluses of 0.5 μg/kg over 10 minutes or lorazepam (0.05–0.1 mg/kg IV every 6 hours) can be added for periodic needs of additional sedation, especially for patients who remain intubated and mechanically ventilated.

Rhythm disturbances are common in the early post-repair periods and in some instances extend as a late complication. Operative recovery can be complicated by supraventricular tachycardia, AV block (intermittent or persistent), and junctional rhythm. Temporary pacing enhances CO for patients with AV block or junctional rhythm in the early postoperative period. A return of normal sinus rhythm can result as myocardial edema resolves and cardiac conduction pathways recover. Ventricular arrhythmias and the risk for sudden death is greatest in the first month after repair with those patients who had perioperative ventricular tachycardia or ventricular fibrillation being at enhanced risk [41]. High-risk patients who have had intermittent ventricular arrhythmias during their early ICU recovery and were treated with IV lidocaine or amiodarone infusions might benefit from continuing oral amiodarone for several months after surgery.

KEY POINTS: EBSTEIN ANOMALY

- Gradually, cyanosis and PBF will improve in symptomatic neonates as PVR decreases.
- Depending on the potential for functional remodelling and relocation of the TV to the true annulus and the adequacy of RV morphology, EA may be remedied by a biventricular repair for less severe forms or palliated with a 1.5 or single-ventricle physiology for more severely affected individuals.
- Patients with extreme cardiomegaly or perioperative ventricular arrhythmias should receive prophylactic antiarrhythmic treatment, such as amiodarone.
- Patients with poorly functioning RVs are dependent upon high filling pressures to maintain adequate CO.

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Tetralogy of Fallot

Incidence, anatomy, and natural history

TOF is the most common cyanotic congenital heart disease with an estimated incidence of 1 in 2,500–3,000 live births [2]. Although reports of this abnormality can be dated back to 1671, it was Etienne Fallot in 1888 who reported the four cardinal distinguishing features and proposed clinicopathophysiologic correlations derived from extensive clinical and postmortem studies. This "blue malady or cardiac cyanosis" as Fallot referred it, was named "tetralogy of Fallot" in 1924 by Maude Abbott [42].

The first surgical treatment for TOF occurred in 1945, when the first Blalock-Taussig shunt (BTS) was performed. The tetrad of TOF consists of (Figure 28.12):

1. RVOT obstruction
2. A large unrestrictive VSD
3. Overriding aorta
4. RV hypertrophy

One embryologic theory states that TOF results from uneven conotruncal spiral septation leading to a smaller MPA and a larger aorta. Another theory, van Praagh's, suggests that the TOF stems from one abnormality – the underdevelopment of the subpulmonary infundibulum (infundibulum means "funnel" in latin). The hypoplastic infundibulum, in turn, affects the surrounding structures as follows: (i) the conoseptum is deviated anterior and leftward contributing to obstruction to flow, (ii) the aorta is shifted rightward over the ventricular septum facing the VSD and facilitates flow of the ejected RV blood into the systemic circulation, (iii) a VSD results from the malaligned conoseptal tissue failing to join the remainder of the ventricular septum, and (iv) postnatal RV muscle hypertrophy develops from cumulative work against the higher pressure load imposed by a stenotic outflow tract and systemic pressure transmitted across the VSD. The phenotype of TOF with PS varies from patient to patient. Although no two TOF cardiac anatomies are the same, physiologically they follow similar guiding precepts for management. Of note, the normal RV of a newborn infant has similar thickness to the LV because of exposure to systemic pressures. As normal cardiac development progresses, the RV becomes thinner relative to the LV as a result of their markedly different afterloads.

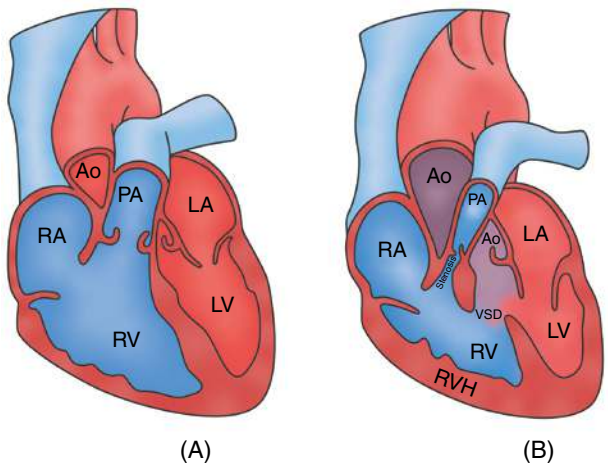


Figure 28.12 Schematic illustration of tetralogy of Fallot. (A) Normal heart. (B) Tetralogy of Fallot demonstrating right ventricle infundibular stenosis (Stenosis), ventricular septal defect (VSD), overriding aorta (Ao), and right ventricular hypertrophy (RVH). LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. (Source: Michael L. Schmitz, MD.)

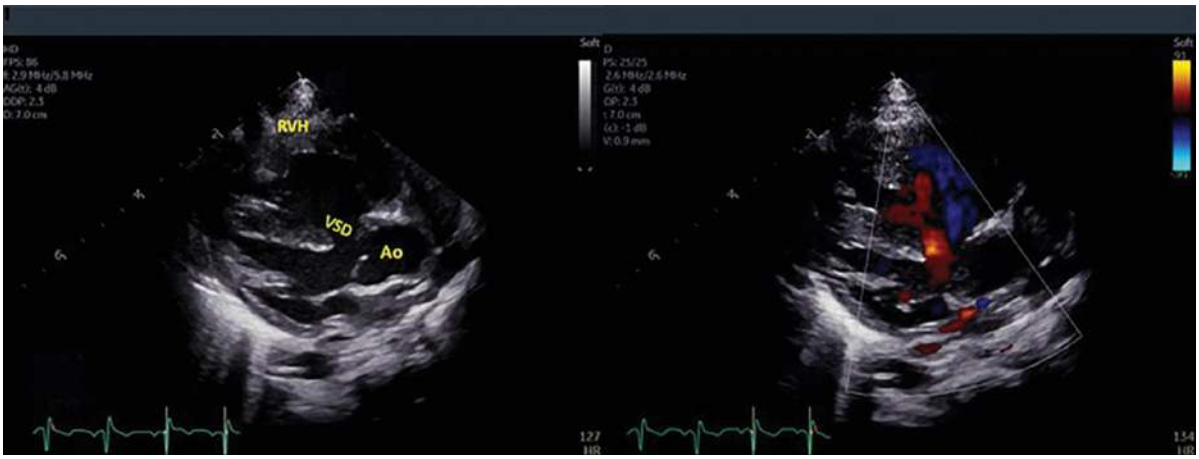
In TOF, the RVOTO often occurs at several levels and has fixed and dynamic components. The fixed obstructions occur at the valvar and supravalvar levels. At the valvar level, the pulmonary annulus is frequently hypoplastic with a bicuspid valve that contains dysplastic leaflets. At the supravalvar level, hypoplasia of the MPA can be localized at the sinotubular ridge or be diffuse and extend into the BPAs. The RVOTO dynamic component comes from the hypertrophied subvalvar muscle bundles. The hypertrophy develops over time in response to the increased pressure load. This dynamic component is thought to play a major role during hypercyanotic episodes associated with TOF. The VSD is usually large and unrestrictive. The bundle of His courses at the posteroinferior edge of the defect, near the anteroseptal leaflet of the tricuspid valve, and can be inadvertently injured during VSD closure [43, 44] (Figures 28.12–28.14).

Other cardiac anomalies associated with TOF are found in about 40% of patients, and they have implications for the optimal surgical repair strategy [44–56] (Table 28.4). Also, anatomical variations influence surgical conduct, e.g. degree of aortic override and location of conoseptum determine the patch size to close the VSD and baffle the LV flow to the aorta [57].

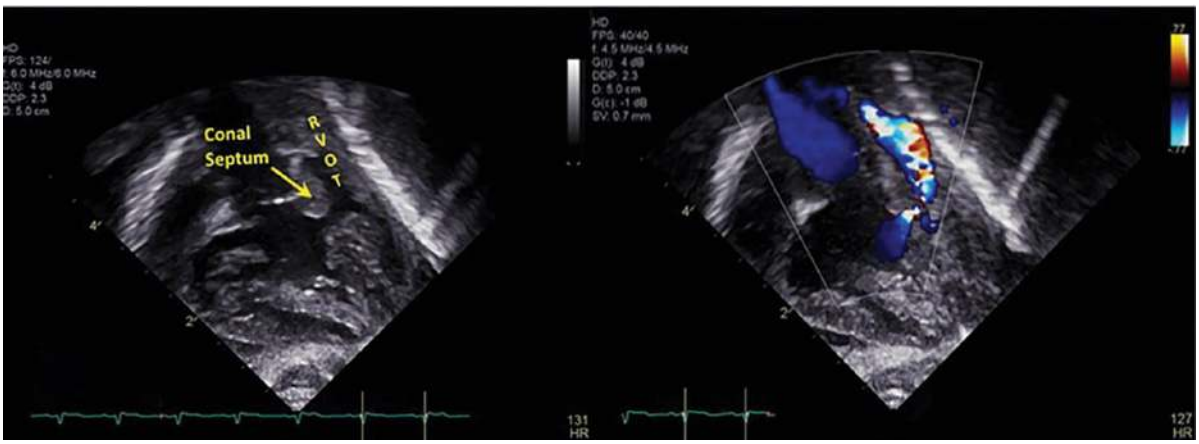
Unique TOF variants include TOF with PA/VSD/MAPCAS (7%) and TOF with absent PV (5%) [58, 59]:

- In TOF with PA/VSD/MAPCAS, total lack of blood throughput leads to severe underdevelopment of the MPA and peripheral pulmonary artery branches such that the MPA may be completely absent, and the BPAs are hypoplastic, non-confluent or even non-existent. MAPCAs often develop to supply blood flow to the lungs. The lungs often show aberrant arborization, unless that side is supplied by a PDA. Some lung lobes have blood supply via BPAs, MAPCAs or both. The surgical approach to this variant varies significantly from that of classic TOF and is described later in this chapter.
- In TOF with absent PV, the PV is ring-like with valve cusp remnants which lead to both stenosis and free pulmonary insufficiency (PI). The MPA, BPAs, and distant peripheral pulmonary arteries are massively dilated, causing compression of the associated airway. The ductus is often absent. Significant tracheobronchial malacia, often with compression, is characteristic of this condition. In severe cases, the newborn presents in respiratory distress and often requires endotracheal intubation with high levels of positive end-expiratory pressure (PEEP) to improve airway patency and decrease air trapping. Prone positioning can also be useful in respiratory management. During surgical repair, the TEE probe has been known to compress the large airways and worsen obstruction. Postoperatively, many patients require long-term ventilatory management due to persistent tracheobronchomalacia and lung disease.

Typically, TOF presents as an isolated lesion, although in 15–30% of patients TOF can present with other abnormalities



(A)

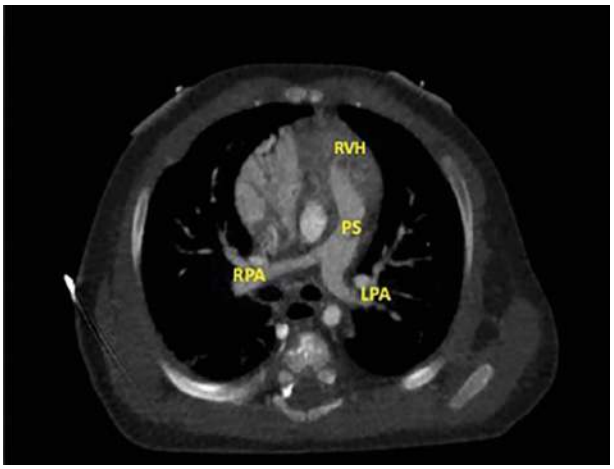


(B)

Figure 28.13 Transthoracic echocardiography images of tetralogy of Fallot. (A) Left image shows ventricular septal defect (VSD), overriding aorta (Ao), and right ventricular hypertrophy (RVH). Right image shows Doppler color flow of left to right shunting through the VSD. (B) Left image reveals anterior deviation of the conal septum with narrowed right ventricular outflow tract (RVOT). Right image Doppler image shows turbulent flow seen through the narrow RVOT. (Source: Destiny F. Chau, MD.)



(A)



(B)

Figure 28.14 Computed tomographic images of tetralogy of Fallot. (A) Sagittal view, demonstrating the overriding aorta (Ao) in brighter contrast. (B) Axial view, showing right ventricular hypertrophy (RVH), pulmonary stenosis (PS), and right pulmonary artery (RPA) hypoplasia. LPA, left pulmonary artery. (Source: Destiny F. Chau, MD.)

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Table 28.4 Cardiac anomalies associated with tetralogy of Fallot and their implications

	Description	Frequency	Surgical Significance	Other Considerations
Coronary artery anomalies	Anomalous and variant coronary artery anatomy can limit options for RVOT patch placement	4.3% anomalous coronary artery (usually the LAD), 6% have a variant infundibular artery originating from RCA crossing the RVOT (Total 10.3%)	Presence of coronary artery over RVOT limits options for RVOT patch and may require RV to PA conduit placement	Direct visual inspection prior to RVOT incision. TTE is usually an adequate primary survey. CT scan can be definitive.
Pulmonary Valve	Frequently bicuspid with thickened leaflets tethered to the pulmonary artery wall	Over 50% are bicuspid	Pulmonary surgical valvotomy for relief of stenosis	Usually, valve will re-stenose after balloon valvuloplasty
Multiple VSDs	Can occur in multiple locations, generally in the muscular septum	5–14%	Suture placement can damage the conduction system. When multiple VSDs are present some may be missed, leading to repeat CPB run to close hemodynamically significant VSDs.	Residual VSDs can result in continued postoperative pulmonary overcirculation. Most muscular VSDs close spontaneously.
Discontinuous Pulmonary Arteries	The proximal LPA near the site of ductal insertion is a frequent location for stenosis. The LPA has ductal tissue that, once regressed, can lead to stenosis or discontinuity of LPA.		Restoration of continuity and/or augmentation of the branch pulmonary arteries is required.	
ASD/PFO	Potential for postoperative atrial level shunting if not closed surgically	Almost always PFO or ASD is present	Often a small opening is left if anticipating postoperative RV dysfunction.	Occasionally included as the pentalogy of Fallot
Right Aortic Arch	Often present with associated abnormal branching of head and neck vessels	25%	Placement of palliative shunts depend on spatial location of aortic branches to pulmonary artery	
Others	• Partial or total anomalous pulmonary venous return • Persistent LSVC • AV septal defect • PDA • Interrupted IVC • Anomalous aortic origin of the coronary artery • Aberrant origin of the right or left pulmonary artery		All might require modifications to the surgical repair, such as an additional venous drainage cannula for a LSVC	

ASD, atrial septal defect; AV, atrioventricular; CPB, cardiopulmonary bypass; IVC, inferior vena cava; LAD, left anterior descending artery; LSVC, left superior vena cava; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RCA, right coronary artery; RV, right ventricle; RVOT, right ventricular outflow tract; TTE, transthoracic echocardiogram; VSD, ventriculoseptal defect.

or as part of a syndrome [60–62]. The most common include the 22q11 microdeletion-associated syndromes called DiGeorge, velocardiofacial syndrome, and conotruncal anomaly face syndrome. Other conditions include trisomy 21 and VACTERL association, among others [60–71] (Table 28.5). There is a mild association of familial inheritance of TOF. Other genetic bases for TOF have been linked to mutations on NKX2-5, JAG1, chromosome 20p12, chromosome 5q35, the GATA4 gene on chromosome 8p23, ZFPM2, TBX1, and GATA6 [72].

The natural course of uncorrected TOF reveals about 50% mortality in the first 5–10 years of life. Prolonged survival is enabled by the persistence of pulmonary flow via the PDA and /or collaterals, and by compensatory hypoxic mechanisms such as erythrocythemia. Uncorrected, it is rare for survival beyond the 4th decade of life. The morbidity and mortality are secondary to chronic hypoxemic ramifications such as thromboembolism, brain abscesses and endocarditis [73].

Modern operative mortality is low with an overall rate of less than 2% in developed countries [74], and less than 4% in low-to-middle income countries [75]. A report analyzing the only collaborative database of congenital heart surgery in

Table 28.5 Syndromes associated with tetralogy of Fallot

*Nearly 1 of 4 of patients with syndromic TOF undergo palliation prior to full repair

Syndrome	Frequency	Associated findings
22q11.2 microdeletion, also known as DiGeorge syndrome, velocardiofacial syndrome and others	7.4–10.5% of all TOF patients or 40–47.8% of the syndromic TOF patients	• 1 per 6000 live births • Variable phenotype • Conotruncal defect (TOF, PA/VSD, IAA, truncus arteriosus) • Immunodeficiency • Neonatal hypocalcemia • Facial and velopharyngeal anomalies • Psychiatric abnormalities
Trisomies: 21, 18, 13	• Trisomies account for 5–7% of all TOF patients • Trisomy 21 is the most common (5.2–5.8% of all TOF patients). • Trisomy 21 was 29–42% of the syndromic TOF patients • Trisomy 18 was 0.8% of the syndromic TOF patients • Trisomy 13 was 0.2% of the syndromic TOF patients	Trisomy 21 • 1 per 700 live births • Cardiac anomalies–the most common is AVC defect • Developmental delay • Congenital hypothyroidism • Hearing loss • Hypotonia Trisomy 18 • 1 per 6,000–8,000 live births • Cardiac anomalies • Respiratory insufficiency • Horseshoe kidney • GI–omphalocele, TEF • CNS–cerebellar hypoplasia, corpus callosum agenesis, spina bifida • Others–micrognathia, microphthalmia, coloboma. Trisomy 13 • 1.9 per 10,000 live births • Cardiac anomalies • Respiratory insufficiency • Renal anomalies • GI- dysphagia • CNS – holoprosencephaly, arhinencephaly, microcephaly, spina bifida • Others–Orofacial clefts, microphthalmia, coloboma
VACTERL association	2.6% of the syndromic TOF patients	• 1 per 10,000–40,000 live births • Vertebral defects • Anal atresia • Cardiac anomalies • Tracheoesophageal fistula, esophageal atresia • Radial and renal dysplasia • Limb abnormalities
CHARGE Syndrome	0.9% of all TOF patients	• 1 per 10,000–100,000 live births • Coloboma • Heart defects • Choanal atresia • Retardation of growth • Genital hypoplasia • Ear anomalies/ deafness
Alagille Syndrome	0.4–1.3% of all TOF patients	• 1 per 30,000 live births • Cardiac defects • Hepatic (bile duct paucity) • Renal anomalies • Skeletal (butterfly vertebrae) • Ophthalmologic findings • Facial abnormalities
Holt-Oram syndrome	0.2% of the syndromic TOF patients	• 0.7–1 per 100,000 births • Congenital heart defects • Upper limb anomalies

AVC, atrioventricular canal; CNS, central nervous system; GI, gastrointestinal; IAA, interrupted aortic arch; PA, pulmonary atresia; TEF, tracheoesophageal fistula; TOF, tetralogy of Fallot; VSD, ventriculoseptal defect.

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low-to-middle income countries found that over half of the children undergoing primary TOF repair were over 1 year of age. Interestingly, age at primary repair was not a risk factor for mortality. Poor nutritional status and hypoxemia were associated with increased infection rates and mortality [75]. Athanasiadis et al. found that syndromic patients with TOF had an all-cause mortality rate of 9.8% [62]. Long-term survival 40 years after TOF repair has been quoted to be over 70% with late mortality from ventricular fibrillation and heart failure [76].

Pathophysiology

Patients with TOF manifest a wide spectrum of clinical presentations depending on the severity of RVOTO and degree of right-to-left shunting of venous blood into the systemic circulation. The unrestrictive VSD allows a near equalization of RV and LV pressures. Shunting direction will be determined by the balance of systemic vascular resistance (SVR) and RVOTO. Most patients are initially asymptomatic and acyanotic – the "pink tets." Some of them have near-normal sized pulmonary valvar and supravalvar areas with minimal RVOTO. As PVR drops, the increasing left-to-right shunting through the unrestrictive VSD leads to pulmonary overcirculation and even CHF. Cyanosis eventually presents at about 6–12 months when infundibular muscles become hypertrophied and RVOTO increases over time. In contrast, some babies present with severe cyanosis shortly after birth and need immediate medical management for stabilization of PBF while preparing for surgical intervention. In these patients, the main obstruction is usually at the level of the PV.

A number of patients develop acute hypercyanotic events or "tet spells," a sudden and profound hypoxemic event that can result in loss of consciousness, stroke, or death. Typically, hypercyanotic episodes occur in association to periods of increased sympathetic activity such as crying, pain and fright. Other predisposing conditions include dehydration, acidosis, and fever – events which decrease SVR and promote right-to-left shunting with resulting arterial desaturation. Additionally, it is postulated that infundibular muscle spasms with acute worsening of RVOTO lead to right-to-left shunting and drastic PBF reduction. The resulting acidosis and hypoxemia decrease SVR, furthering the right-to-left shunting. Prompt aggressive treatment to halt the vicious cycle, reverse the shunt, and restore pulmonary flow is imperative. Treatment for hypercyanotic episodes is described later in the chapter. During these events, awake patients often hyperventilate, likely to mitigate the hypoxia and acidosis. Squatting behavior during the spell is also observed in older children. Squatting increases SVR from compression of the iliac arteries, increasing RV preload with enhanced venous return generated by elevating intraabdominal pressure and compressing veins in the leg musculature. The result of squatting is reduced right-to-left intracardiac shunting and increased PBF.

Progression of infundibular and RV hypertrophy from exposure to high pressure loads results in anatomical changes that complicate the perioperative course and contribute to postoperative RV dysfunction: (i) the RV becomes less compliant with abnormal diastolic relaxation, requiring high filling pressures for adequate CO, (ii) the hypertrophied RV and muscle bands increase surgical complexity, (iii) the increased RV muscle mass may reduce the myocardial protection of cardioplegia, a reduction in protection that in some instances is compounded by abnormal coronary artery distributions, and (iv) muscle resection or division is often required to relieve the RVOTO.

Presently, complete surgical correction is commonly performed in early infancy for most patients. Early repair is thought to prevent the development of RV hypertrophy, minimize the effects of cyanosis and polycythemia, allow improved pulmonary vascular development via greater PBF, and avoid the occurrence of hypercyanotic episodes.

Fetal ultrasonography can diagnose TOF prenatally. After birth, most neonates with TOF are acyanotic and present with non-specific physical examination findings. Auscultation shows a crescendo–decrescendo systolic murmur best heard at the left upper sternal border prompting further investigation. Clubbing is not a feature at this stage; it only becomes apparent after prolonged periods of chronic hypoxemia. Ductal closure will uncover cyanosis in those with severe PS and ductal-dependent PBF. The ECG reveals persistent RV hypertrophy and right axis deviation beyond the neonatal period. The chest radiograph shows a "boot-shaped" cardiac silhouette, resulting from the RV hypertrophy displacing the apex upwards and the hypoplastic MPA creating a concave upper left heart border. Transthoracic echocardiography is effective at establishing the TOF diagnosis and demonstrating related important features: (i) extent and anatomical characteristics of RVOTO, (ii) VSD size, number and locations, (iii) coronary artery distribution, (iv) additional cardiac abnormalities including ASD and aortic arch-sidedness, and (v) biventricular function.

Most children are diagnosed during infancy in countries with routine access to modern medicine. In regions of the world with limited access to care, it is common to see children with uncorrected TOF present at much older ages with advanced pathology.

Surgical and transcatheter approaches and outcomes

Initial stabilization and planning for intervention

All infants born with TOF eventually require intervention as hypoxemia develops. Most patients can be monitored until meeting indications for surgery that occurs when the oxygen saturation declines below 75–80% or with the advent of hypercyanotic episodes. If delaying surgery is necessary, patients manifesting hypercyanotic episodes can sometimes be temporized with propranolol.

For patients with significant cyanosis who have contraindications to surgery, a palliative balloon dilation and/or stenting of the PDA or RVOT can be performed in the cardiac catheterization laboratory [77]. Surgical palliation via a modified BTS (mBTS) is also an option for patients who are deemed too high risk or have unfavorable anatomy to undergo early primary repair. A palliative shunt allows time for optimization of surgical conditions including time for corporal growth; complete repair is facilitated when performed on a larger-sized heart and infant. This two-stage repair (palliative systemic-to-pulmonary artery shunt

followed by later full repair) comes with the risks associated with an additional thoracic surgery as well as risks of loss of shunt patency, imbalance of PBF to systemic blood flow ratio (Qp:Qs), and distortion of pulmonary arterial anatomy.

Factors influencing the surgical approach and timing are based on the patient's symptomatology, cardiac anatomy, concomitant risk factors, the center's capability and preferences, and contraindications to early complete repair. Elective complete repair in the neonate is currently performed in some centers. The smaller anatomy makes the operation more challenging; many use a ventriculotomy to facilitate surgical exposure as opposed to a transatrial or transpulmonary approach. Additionally, the neonate's immature organ systems are subject to the negative effects of CPB. Other concerns of neonatal full repair are associated with increased longitudinal morbidity [78, 79]. For elective cases, some centers prefer the staged approach while other centers favor elective complete primary repair between 3 and 6 months of age [78]. Current survival rates after complete repair of TOF are over 98%. Although the optimal TOF repair strategy is unclear, the preservation of the PV and supporting structures while reducing RVOTO are key determinants for reducing long-term morbidity. Morales et al. have proposed a surgical decision algorithm with the goal of preserving the RV and infundibulum [80, 81] (Figure 28.15). Results for this approach appear promising [81, 82].

Surgical and transcatheter palliation

Palliation, meaning "lessening the intensity of disease," comes from the late Latin word "palliatus," meaning to cloak or to mask. A palliative intervention does not offer correction but rather a relief for a condition, generally only temporary. For TOF, the first operative procedure was palliative, the classic BTS by Blalock in 1945, an end-to-side anastomosis of the subclavian artery to the right pulmonary artery branch, to provide a source of pulmonary flow. The anastomosis is usually performed on the side ipsilateral to the innominate artery. Direct anastomotic aorto-pulmonary shunts, such as the now nearly obsolete Potts and Waterston shunts, are difficult to take down due to their anatomical locations. The mBTS is the most commonly used systemic-to-pulmonary shunt (Figure 28.16). It consists of prosthetic graft placed between the innominate artery or the subclavian artery and the ipsilateral BPA. When anatomy is unfavorable for a mBTS, a central shunt, comprising a graft placed between the ascending aorta and the MPA, may be placed. In TOF, the shunt augments PBF until complete primary repair can be achieved. The mBTS allows early palliation without sacrificing the subclavian artery. Resistance from the graft diameter (usually 3.5–4 mm) and length regulates PBF. The locations of the mBTS and central shunts allow exposure and maneuverability during subsequent repairs. A right-sided mBTS is most common due to more favorable surgical exposure during take down and less risk of phrenic nerve injury compared to a left-sided mBTS. Although mBTS was traditionally done via a thoracotomy, many centers are performing mBTS via median sternotomy. This approach also facilitates patch augmentation of narrowed BPAs with bypass support. A downside of a mBTS is that the shunt can frequently lead to stenosis and distortion of the BPA [44].

Patients who are unsuitable candidates for surgical palliative shunts, often small and critically ill neonates or infants, can undergo the less invasive transcatheter palliative interventions such as pulmonary balloon valvuloplasty and stent placement in the RVOT or PDA to maintain PBF. Candidates for ductal stenting have an anatomically suitable ductus as well as an additional source of PBF. Pulmonary balloon valvuloplasty alone seldom produces long-lasting improvement, as the dilated RVOT often returns to its original stenotic state. Cutting balloons or primary stent implants are associated with longer-lasting improvement in relief of obstruction. Application of stents should be done in consultation with the cardiac surgeons as the stents impact the operative conduct of the full repair [52, 83, 84]. See Chapters 19 and 34 for further discussion of RVOT and PDA stenting.

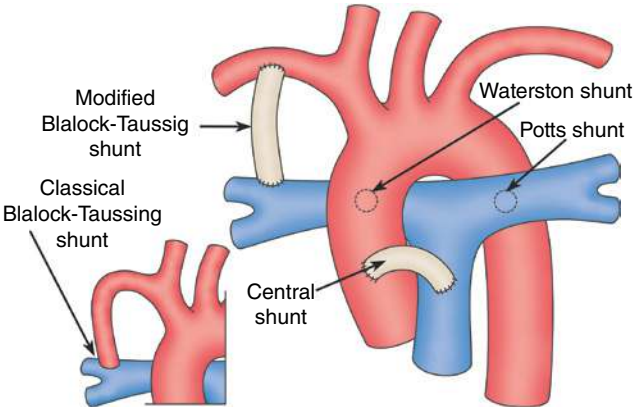


Figure 28.16 Diagram showing the various types of shunts used to increase pulmonary blood flow. The modified Blalock–Taussig shunt and the central shunt are the only shunts used in the modern era. (Source: Michael L. Schmitz, MD.)

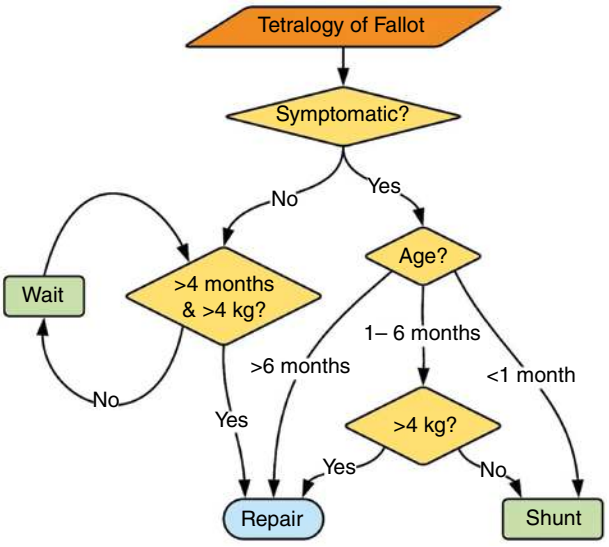


Figure 28.15 Algorithm for treatment of TOF as described by Morales et al. [80]. (Source: Schmitz et al. [38]. Reproduced with permission of John Wiley & Sons.)

Surgical repair

Preoperative knowledge of pertinent anatomic TOF details is important for surgical planning and successful repair, including size and nature of RVOTO at the subvalvular, valvular, and supravalvular levels, coronary artery distribution, type and number of VSDs, and any other associated cardiac anomalies.

The first successful full repair of TOF was performed on a 10-year-old boy by Walton Lillehei in 1954. In the early era of TOF repair, the goals of surgery were relief of RVOTO and VSD closure via ventriculotomy while preserving RV function. In the 1960s, full repair was reserved for children 4–6 years of age because surgical mortality was too high for younger patients. Later, use of deep hypothermic circulatory arrest improved survival and opened the door for full primary repair during infancy.

Early repair has hemodynamic and anatomic advantages for the developing heart. Although some centers offer neonatal elective full repair, most centers prefer to perform elective full primary repair between 3 and 6 months of age and prior to 12 months for those with a palliative shunt. The increased duration of longitudinal postoperative follow-up reveals that adults with repaired TOF exhibit medical and surgical sequelae such as impaired exercise capacity, atrial and ventricular arrhythmias, RV and LV dysfunction, cardiac failure, and sudden death. The pathophysiology of these late complications appears related to the effect of extensive ventriculotomy, coronary artery compromise and PV destruction. Findings from outcomes have led to changes in the surgical approach by emphasizing the preservation of the RVOT apparatus, sparing PV injury, minimizing ventriculotomy incisions, and reducing residual VSDs. Hence, transatrial and transpulmonary approaches with valve-sparing techniques are emphasized with only selective use of transannular patches (Figure 28.17). The surgical approach is via median sternotomy with CPB-assist. The thymus size is noted prior to subtotal excision due to association to 22q11.2 microdeletion syndromes with TOF.

Upon cardiac exposure, the coronary artery distribution is assessed. After CPB commencement and cardioplegia, the RVOT is examined through a right atriotomy via the TV, and the PV annulus is sized with calibrated dilators. Muscle bundles are divided as needed. A PV commissurotomy can be performed transatrially if exposure is adequate; otherwise, it can be accessed via a transpulmonary approach by a longitudinal incision in the MPA. If preservation of the PV is not feasible, a right ventriculotomy with placement of transannular patch will be done to augment the RVOT size. The VSD is closed using a patch, avoiding the AV node or bundle of His that passes adjacent to the VSD margin. The atrial level shunt is closed if present. If postoperative RV dysfunction is expected, a small atrial communication ("pop-off") is left to allow LV filling and preload with a degree of right-to-left shunting. Patch augmentation of BPA stenosis is performed as needed. In some patients, a RV-to-pulmonary artery conduit may be necessary to avoid injuring a coronary artery crossing the RVOT (Figure 28.18). TEE is used after separation of CPB to assess for adequacy of repair, residual shunts and defects, and ventricular function. An RV:LV pressure ratio greater than 0.7 usually indicates inadequate relief of RVOT obstruction, with the caveat that early post-CPB pressure measurements do not always correlate to later measurements and might prompt unnecessary revisions. If residual shunts are suspected, a comparison of PaO_2 from simultaneous blood gas measurements taken from the superior vena cava and the MPA can be helpful. Temporary atrial and ventricular pacing wires are placed prophylactically for the management of postoperative arrhythmias such as heart block and junctional ectopic tachycardia (JET) following TOF repair.

Long-term surgical complications

Most patients with repaired TOF will live to adulthood; however, many will require reintervention before 30 years of age to address residual disease. The most common sequela is PI. Other sequelae include BPA stenosis, residual VSDs, and RVOT aneurysmal dilation. Chronic PI leads to RV volume overload, RV dilation and dysfunction, and ventricular arrhythmias. Eventually, these sequalae affect the LV and cause biventricular dysfunction and heart failure. Monitoring

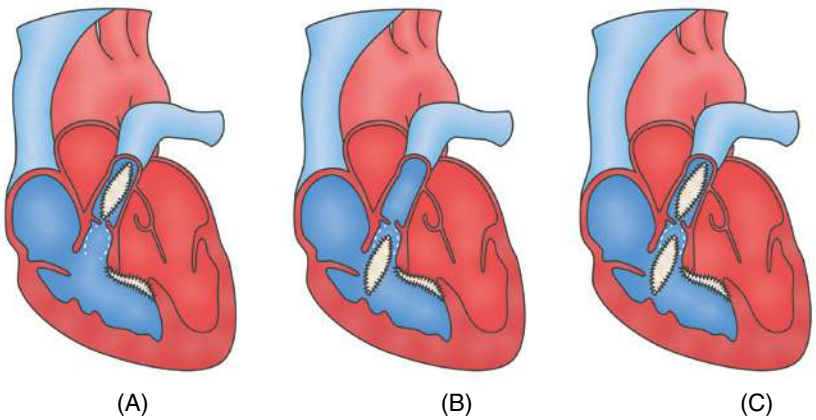


Figure 28.17 Surgically repaired hearts with tetralogy of Fallot, showing resection of right ventricular outflow tract (RVOT) muscle (dashed lines), patch closure of the ventricular septal defect (VSD), and patch arterioplasty: (A) supravalvular main pulmonary patch arterioplasty, RVOT muscle resection, VSD patch; (B) RVOT patch, RVOT muscle resection, VSD patch; (C) supravalvular main pulmonary patch arterioplasty, RVOT patch, RVOT muscle resection, VSD patch. (Source: Michael L. Schmitz, MD.)

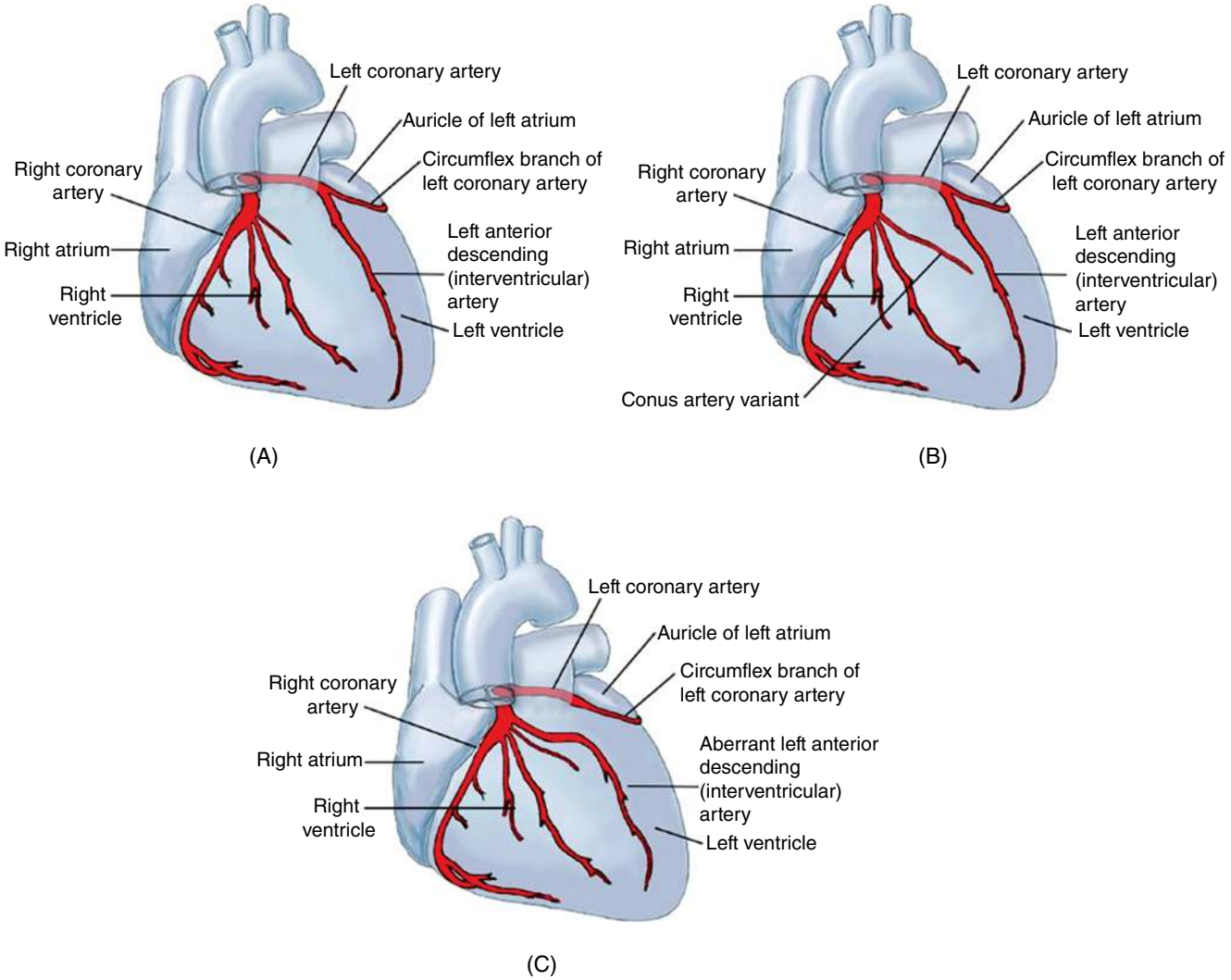


Figure 28.18 (A) Normal coronary artery pattern, (B) Normal variant conal artery (first branch of right coronary artery) crossing the right ventricular outflow tract, (C) Aberrant left anterior descending artery arising from right coronary artery and crossing the right ventricular outflow tract. (Source: Michael L. Schmitz, MD.)

for symptomatology and progression of RV dilation is essential. An increasingly used monitoring modality is cardiac MRI for the longitudinal evaluation of volumetric ventricular measurement, PI fraction quantification, and RV functional status [85]. Ideally, a PV replacement is performed prior to irreversible RV dysfunction from the effects of PI but as late as possible to allow placement of an adult-sized valve to decrease the number of re-interventions needed in a patient's lifetime. Bioprosthetic valves deteriorate over time, and most patients will require another replacement within a decade. For symptomatic patients, PV replacement is indicated. For asymptomatic patients, the timing and indications for PV replacement is unclear. Professional organizations have published criteria to guide these decisions [86].

Transcatheter pulmonary valve implantation

Multiple PV interventions are needed over the lifetime of the TOF patient. The most common late re-intervention in the patient with repaired TOF is PV replacement. Nonsurgical options for PV replacement are currently available as transcatheter valve implants for patients with dysfunctional RV-to-pulmonary artery conduits, such as the Medtronic Melody valve (Medtronic, Inc., Minneapolis, MN), a stent-mounted bovine jugular valve and the Edwards SAPIEN XT valve (Edwards Lifesciences Corporation, Irvine, CA), a stent-mounted bovine pericardial valve. Pre-stenting a RV-to-pulmonary artery conduit to prepare a landing zone for the PV to anchor is often necessary (Figure 28.19). Transcutaneous valves for the native RVOT without a circumferential conduit are under development. Knowledge of coronary artery location is necessary to avoid coronary artery compression during and after valve implantation. Other than coronary artery compression, complications include stent fracture, RV-to-pulmonary artery conduit tear, device dislodgement and infective endocarditis. This field continues to grow, and more transcutaneous device options will become available [87]. See Chapter 34 for additional discussion of transcatheter PV implantation.

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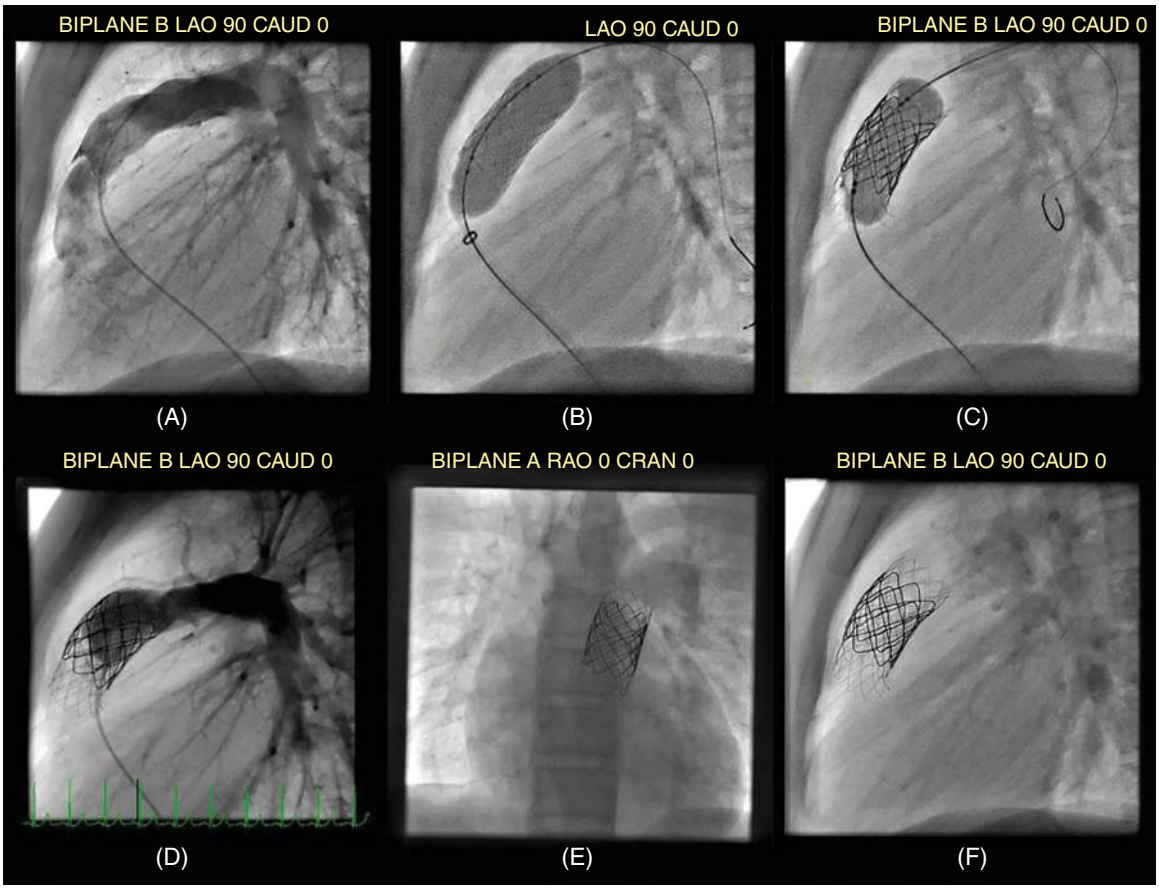


Figure 28.19 Transcatheter Pulmonary Valve Implantation. (A) Contrast injection of right ventricle-to-pulmonary artery conduit showing pulmonary insufficiency and irregular luminal surface, lateral view. (B) Pre-stenting of right ventricle-to-pulmonary artery conduit for improved landing surface for the pulmonary valve to anchor, lateral view. (C) Pulmonary valve deployment inside of right ventricle–pulmonary artery conduit pre-stent, lateral view. (D) Contrast injection showing a competent pulmonary valve, lateral view. (E) Final pulmonary valve position, anterior to posterior view. (F) Final pulmonary valve position, lateral view. (Source: Destiny F. Chau, MD.)

Anesthetic considerations

Initial assessment and planning

Hypoxemia becomes progressive over time as PBF diminishes concordant to the increasing obstruction by the RVOT. Some patients experience hypercyanotic episodes when the oxygen saturation acutely drop to 20–30% or less. Since systolic pressure in the RV reflects the pressure in the LV and aorta, a decrease in systemic arterial pressure (as may occur with peripheral vasodilatation caused by anesthetic agents and sedative drugs, or prolonged fasting) results in decreased RV pressure and PBF. An increase in LV pressures, as induced by vasoactive agents and volume administration, can reverse shunting of blood from the RV into the LV and promote PBF. Close monitoring of blood pressure changes from anesthetic interventions can provide early physiological guidance for optimizing PBF and preventing hypercyanotic episodes.

Preoperative assessment should include the history of hypercyanotic episodes in patients who are not palliated or repaired. Patients with severe cyanosis present with failure to thrive and polycythemia unless they are anemic. Polycythemia actually enhances the "blueness" during hypercyanotic episodes due to higher levels of deoxygenated hemoglobin. Patients with stable and mild cyanosis often have had generous weight gain from frequent feedings given to prevent agitation and worsened cyanosis. Anticipation, early recognition, and management of potential hypercyanotic episodes are essential for avoiding cardiovascular collapse.

Preoperatively, the following factors are considered for preventing hypercyanotic episodes:

- Minimize patient agitation to reduce tachycardia, increased infundibular tone and increased oxygen consumption. Keep the patient at ease by avoiding irritating events; use premedication in a monitored setting and comfort the infant as needed (e.g., judicious use of sugar drops or a pacifier may mitigate hunger).
- Minimize dehydration by avoiding prolonged fasting. Offer clear fluids up to 1–2 hours prior to anesthesia induction or administer IV fluids if IV access is present.
- Beta blocker therapy should be continued as prescribed.

Even under anesthesia, increased stimulation can incite infundibular spasm that enhances right-to-left shunting, precipitating a hypercyanotic episode. Anesthetic induction and

times of surgical manipulation are especially vulnerable periods for occurrence of a hypercyanotic episode. Infants with unrepaired TOF may present for anesthetic care for non-cardiac interventions such as cardiac catheterizations, MRI, and CT, or for surgical procedures that cannot be delayed until cardiac palliation or repair (Table 28.6).

Management of hypercyanotic episodes

The primary goal is to improve PBF so that the hypoxemia can be reversed. PBF is increased by reducing acute RVOT obstruction promoted by the infundibular spasms, enhancing RV preload, and reversing right-to-left intracardiac shunting by increasing SVR relative to RV pressure. The

Table 28.6 Overview of considerations and recommendations for the anesthetic management of patients with unrepaired tetralogy of Fallot (TOF), acyanotic or cyanotic, for non-cardiac surgery

Anesthesia considerations and recommendations for patients with unrepaired TOF undergoing non-cardiac surgery	
Acyanotic, "Pink Tets," at risk for pulmonary overcirculation	**Cyanotic, "Blue Tets," at risk for hypercyanotic spells**
Hemodynamic goal: Maintain Qp:Qs near 1:1 1. Avoid increased left to right shunt and worsening of pulmonary overcirculation. 2. Maintain awareness that the shunt can reverse in situations of increased PVR (hypoxia, hypercarbia, acidosis, hypothermia)	**Hemodynamic goal**: Preserve PBF and avoid hypercyanotic episodes 1. Avoid tachycardia, dehydration 2. Maintain adequate preload to counteract stiff RV and decrease RVOTO 3. Maintain SVR to minimize right to left shunt & promote PBF 4. Avoid sudden catecholamine release, maintain appropriate anesthetic depth
FiO_2 restrictions- Avoid unnecessary hyperoxia as it increases PBF	**FiO_2 restrictions**- None
PREOPERATIVE 1. Premedicate as needed for anxiolysis. 2. Avoid prolonged fasting. Patients may be on diuretics for CHF.	**PREOPERATIVE** 1. Premedicate as needed for anxiolysis to avoid hypercyanotic episodes prior to induction 2. Avoid unnecessary fasting to maintain preload.
INTRAOPERATIVE **Monitors/Lines** 1. Standard ASA monitors with 5-lead ECG 2. De-air all lines to avoid paradoxical embolism. 3. +/– invasive arterial line or central line as warranted by extent of surgery and anticipated hemodynamic perturbations.	**INTRAOPERATIVE** **Monitors/Lines** 1. Standard ASA monitors with 5-lead ECG 2. De-air all lines to avoid paradoxical embolism. 3. +/– invasive arterial line or central line as warranted by extent of surgery and anticipated hemodynamic perturbations.
Anesthesia induction 1. Inhalation induction, sevoflurane +/– nitrous oxide, +/–IM ketamine and rocuronium as needed 2. Place IV after induction. 3. If IV → ketamine (1–2 mg/kg) +/– fentanyl (1–2 mcg/kg) +/– sevoflurane. Intubate after paralysis. **SBE prophylaxis as indicated	**Anesthesia induction** 1. Inhalation induction sevoflurane +/– nitrous oxide, +/–IM ketamine and rocuronium as needed 2. Place IV after induction. 3. If IV → ketamine (1–2 mg/kg) +/– fentanyl (1–2 mcg/kg) +/– sevoflurane. Intubate after paralysis. **SBE prophylaxis as indicated
Anesthesia maintenance 1. Inhaled anesthetic agent (sevoflurane). Titrate dexmedetomidine. 2. Volume replacement to maintain euvolemia. Used blood products as needed to compensate for surgical blood loss, maintain organ perfusion and optimize hemostasis	**Anesthesia maintenance** 1. Inhaled anesthetic agent, sevoflurane. Titrate dexmedetomidine. 2. Volume replacement often needed to maintain preload, with higher filling pressures for a stiff RV. Used blood products as needed to compensate for surgical blood loss, maintain organ perfusion and optimize hemostasis.
Anesthesia emergence 1. If extubation planned, optimize pain control with adjuvant acetaminophen, regional block or local anesthetic infiltration. Titrate dexmedetomidine to adequate sedative effect. 2. If postoperative mechanical ventilation planned, prepare for sedation for transport to ICU.	**Anesthesia emergence** 1. If extubation planned, optimize pain control with adjuvant acetaminophen, regional block or local anesthetic infiltration. Titrate dexmedetomidine to adequate sedative effect. 2. If postoperative mechanical ventilation planned, prepare for sedation for transport to ICU.
Postoperative care 1. ICU or stepdown ICU if extubated 2. ICU care if mechanically ventilated	**Postoperative care** 1. ICU or stepdown ICU care if extubated 2. ICU care if mechanically ventilated

ASA, American Society of Anesthesiologists; CHF, congestive heart failure; ECG, electrocardiogram; IM, intramuscular; IV, intravenous; PBF, pulmonary blood flow; PVR, pulmonary vascular resistance; Qp, pulmonary blood flow; Qs, systemic blood flow; TOF, tetralogy of Fallot; RV, right ventricle; RVOTO, right ventricle outflow tract obstruction; SBE, subacute bacterial endocarditis; SVR, systemic vascular resistance.

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Table 28.7 Treatment for a "tet spell" or hypercyanotic episode for patients with tetralogy of Fallot

- Increase RV preload – dilate the right ventricular outflow tract and improve cardiac output
  - Give IV fluids
  - Apply knee-chest position or abdominal compression
  - Directly compress aorta via open chest
- Increase SVR – Reverse right to left shunt
  - Administer phenylephrine 5–10 mcg/kg IV
  - Apply knee-chest position or abdominal compression
  - Directly compress aorta via open chest
- Decrease infundibular spasm via negative inotropic effects
  - Administer sedatives
  - Administer beta-blocker drugs (e.g., esmolol 50 mcg/kg, and then titrate to effect)
  - Increase depth of anesthesia; if inhaled agent, use sevoflurane
- Decrease pulmonary vascular resistance by reducing hypoxic pulmonary vasoconstriction
  - Increase inhaled oxygen
- Avoid tachycardia – increase diastolic filling time and improve right ventricular preload
  - Administer sedatives
  - Administer beta-blocker drugs

RV, right ventricle; IV, intravenous; SVR, systemic vascular resistance; ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass.

objectives are to increase afterload to the left heart, reduce RV infundibular spasm, and augment RV preload (Table 28.7).

If the patient remains cyanotic despite these measures, ECMO should be considered as a lifesaving therapy. Sternotomy with manual compression of the aorta can be used to temporarily increase SVR and reverse right-to-left shunting while rapidly instituting CPB.

Perioperative anesthetic management for surgical palliation

Most neonates or infants needing surgical palliation are critically ill and dependent on PGE_1 infusion to maintain ductal patency for augmenting PBF and managing hypoxemia. Some other infants become symptomatic shortly after discharge from the hospital as they develop cyanosis and fail to thrive. Anesthetic goals are to maintain PBF by limiting right-to-left intracardiac shunting and preserving adequate SVR. Induction of anesthesia can be successful with ketamine and/or fentanyl with an inhaled agent for maintenance. General anesthesia and potent inhaled agents have been demonstrated to depress ventricular function [88, 89]. Rivenes et al. showed that both sevoflurane and isoflurane have a dose-dependent, albeit not statistically significant, decrease in CO and shortening fraction at 1 and 1.5 MAC. Isoflurane led to larger dose-dependent increases in heart rate and decreases in SVR index compared to sevoflurane; thus, sevoflurane would be the better choice [90]. IV fluids and phenylephrine are useful to increase SVR. Inotropic drugs can increase heart rate and contractility and worsen infundibular spasms. In the absence of reliable IV access, inhalational induction with sevoflurane, and intramuscular ketamine and rocuronium as needed can provide adequate conditions for IV access and tracheal intubation. Central venous access is obtained for the infusion of fluids and vasoactive agents. An arterial line is placed for close hemodynamic monitoring and blood gas sampling. If placing a radial arterial line, it is recommended on the contralateral side of the anticipated mBTS, so that blood pressure assessment is unbiased by the run-off from the ipsilateral innominate artery or by possible stenosis at the anastomotic site.

Although mBTS was traditionally done via a thoracotomy, the mBTS is now often performed via median sternotomy [47]. Median sternotomy permits exposure for conversion to a central shunt, institution of CPB in the event of severe hemodynamic instability or need to patch augment the BPAs, inspection of the coronary anatomy, division of the PDA while confirming adequacy of the shunt flow, and avoidance of a separate incision site after full repair. Median sternotomy also avoids the lung retraction required for exposure with thoracotomy. Heparin at 100 units/kg is given prior to shunt placement. Hypoxemia and hemodynamic instability can occur during the partial clamping for the graft anastomosis and is managed with vasoactive support, fluids, and ventilatory adjustment. Once the shunt is open, oxygen saturation acutely improves while blood pressure decreases. A widened pulse pressure gradient results due to low diastolic pressure secondary to blood run-off to the lungs; insufficient diastolic blood pressure can compromise coronary perfusion. Management with normoventilation, low FiO_2, volume, and vasopressors can temporize this problem. If a mBTS was done via a right thoracotomy and a PDA was present, the excessive diastolic run-off may continue until the PDA closes. PGE_1 infusion is discontinued when alternative PBF is established. A shunt flow approaching Qp:Qs of 1:1 under normal physiological conditions of normocarbia while breathing spontaneously in room air is ideal, resulting in an SpO_2 of 80–85% in the absence of parenchymal lung disease. Intraoperatively, simulating normal physiological conditions as closely as possible is important for accurate clinical assessment of Qp:Qs. If the ductus is still open, the additional PBF must be considered in Qp:Qs. Otherwise, saturations too high or too low would indicate an imbalanced Qp:Qs. Lower than expected saturations, after ruling out reversible ventilatory impairments such as atelectasis or endobronchial intubation, may indicate that the shunt is inadequate. Some surgeons prefer the larger diameter shunts if physiologically tolerated to accommodate patient growth and associated increased PBF needs prior to the full repair. Platelet transfusions are avoided whenever possible due to an increased risk of shunt thrombosis.

Postoperative care for surgical palliation

In the ICU, the patient is supported with mechanical ventilation for the next 12–24 hours for stabilization, monitoring and management of ongoing physiologic changes. Potential complications include unilateral or bilateral pulmonary edema or hemorrhage from increased PBF. Also, low systemic diastolic blood pressure can compromise coronary artery flow during diastole, causing myocardial ischemia. Shunt thrombosis is always a potential risk, and heparin infusion at 6–10 units/kg/hour is commenced to maintain

shunt patency after the risk of surgical bleeding subsides. A shunt murmur, reflecting presence of shunt blood flow, can be easily auscultated by pausing ventilation and placing the stethoscope at the end of the endotracheal tube; the murmur is transmitted via the endotracheal tube because the shunt is near the bronchus. Antiplatelet therapy is initiated with aspirin when enteral intake is started and continued until the time of complete repair. Other perioperative complications include recurrent laryngeal nerve and phrenic nerve damage and development of chylothorax from thoracic duct injury.

Perioperative anesthetic management for surgical repair

The pre-CPB goal is the promotion of PBF, and post-CPB goals are preservation of ventricular function and CO optimization. Monitors include central venous pressure and invasive arterial blood pressure. Cerebral oximetry is helpful. TEE is recommended post-CPB to assess the surgical repair, but epicardial echocardiography can be used if TEE is not feasible.

Induction of anesthesia for complete repair can be similarly accomplished as for the palliative shunt placement. For patients at a low risk of hypercyanotic episodes, inhalational induction of anesthesia is generally safe. There are several described techniques for maintenance of anesthesia. If immediate extubation in the operating room or early extubation in the ICU (within 6 hours after surgery) is anticipated, then a multimodal low-dose opioid technique is recommended. At the author's institution, a technique of total fentanyl dose of 10–15 μg/kg supplemented with an inhalational agent, dexmedetomidine infusion 0.3–0.5 μg/kg/hour, morphine infusion 20–25 μg/kg/hour, local anesthetic wound infiltration and IV acetaminophen provide for adequate immediate extubation conditions after surgical closure. The extubated patient is transported to the cardiac ICU with continuation of the dexmedetomidine and morphine infusions, as well as a milrinone infusion. A report compared three anesthetic techniques in patients 30 days-old to 3 years-old undergoing TOF, AV canal or ASD repair: fentanyl 10 μg/kg vs. fentanyl 25 μg/kg vs. fentanyl 10 μg/kg plus dexmedetomidine at 1 μg/kg loading dose followed by 0.5 μg/kg/hour infusion, until separation from CPB. Adjuvant isoflurane was used in all three groups. It showed that the stress response, coagulopathy, transfusion requirements and postoperative opioid use were highest in the fentanyl 10 μg/kg group while the stress response was most blunted with the 25 μg/kg fentanyl dose. Adding dexmedetomidine to the low-dose fentanyl group improved stress response blunting and provided better postoperative pain control. No difference in timing for fast track extubation was found amongst all three groups [91]. One institution described using a ketamine infusion and found more hemodynamic stability when compared with isoflurane due to preservation of SVR in the pre-CPB period [92].

Considerations for separation from CPB include:

- *RV dysfunction* can occur especially if a ventriculotomy was performed. Pre-existing RV hypertrophy and diastolic dysfunction may require high filling pressures to maintain CO. Management should target increasing preload, decreasing RV afterload, and adding inotropic support such as milrinone (0.375–0.75 μg/kg/min) and perhaps low dose epinephrine (0.02–0.04 μg/kg/min).
- *A hyperdynamic RVOT* may be observed especially during periods of tachycardia, limiting stroke volume. Management includes decreasing the heart rate with an esmolol infusion in the early postoperative period while maintaining adequate preload.
- *Tachydysrhythmias* occur frequently after complete TOF repairs. A recent review found an overall frequency of 19% in a multi-institutional database of 7749 patients [93]. Surgical repair frequently disrupts the conduction system located in close proximity of the VSD. JET is a narrow complex tachydysrhythmia originating from the AV node and His bundle area; it often develops within 24 hours after repair and has been associated with increased length of stay [94]. JET is characterized by heart rates above 170/min and AV dissociation leading to significant hemodynamic instability. Risk factors include young age, long CPB and aortic cross clamp times, preoperative tachycardia, high inotropic requirements, and surgical intervention near the AV node. Treatment consists of sedation, electrolyte correction, cooling to 34–35 °C, and IV amiodarone [56, 95]. A meta-analysis showed that a prophylactic dexmedetomidine infusion was effective in reducing postoperative JET [96]. Another study showed that dexmedetomidine has increased preventive effects when started preincision [97]. Prophylactic amiodarone has also been reported to reduce the incidence of JET [98]. Heart block is common after separation of CPB. The heart block may be transient due to inflammation around conduction fibers. A temporary pacemaker is helpful while awaiting recovery of normal cardiac conduction. In some patients, recovery is not seen until for 7–10 days; afterward, a permanent pacemaker is considered. Many patients demonstrate right bundle branch block on postoperative ECG, particularly those who underwent ventriculotomy.
- *Coagulopathy and bleeding* after separation of CPB is common after TOF repair. Hemodilution of coagulation factors and platelets, pronounced inflammatory effects of CPB and immature coagulation systems increase the risks for bleeding in small, young patients undergoing early TOF repair. Transfusion of multiple component blood products is almost always required for this patient group. It is not surprising that a recent Society for Thoracic Surgeons (STS) Congenital Heart Surgery database analysis showed a consistent median greater than 99% for intraoperative blood transfusion for all patients 30 days and younger and those aged 31 days to 12 months across 82 centers [99]. The use of antifibrinolytics such as epsilon-aminocaproic acid or tranexamic acid have been shown to reduce post-CPB bleeding and minimize the use of blood products. Aprotinin, a protease inhibitor antifibrinolytic, is no longer available in the US; however, it is available in Europe.
- *Residual VSDs* appear to be common. Small VSDs are usually hemodynamically insignificant and are likely to close spontaneously. If greater than 2–3 mm, excessive PBF will be poorly tolerated and it may be necessary to resume CPB for further VSD closures after quantification of the shunt magnitude by echocardiography and hemodynamic evaluation [100, 101]. Also, some VSDs that were undetected preoperatively due to equalization of ventricular pressures may be now visualized after relief of the RVOT obstruction.

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The degree of additional shunting and hemodynamic significance may indicate a return to CPB.

Indications for returning to CPB include coronary compromise by excessive traction or injury, residual VSDs, residual RVOT obstruction and TR.

An STS database report found that early extubation (within 6 hours after surgery) was performed in 31.5% (478 of 1,519) of children undergoing TOF repair between 2010–2013, in an aggregate of 92 centers [102]. An updated report from 2010–2017 found that 17.15% (705/4126,120 programs) of TOF repair patients were extubated before leaving the operating room [103]. Although early tracheal extubation has associated advantages such as avoidance of positive pressure ventilation and shorter lengths of ICU and hospital stay, patient selection and the implementation of strong strategies for managing postextubation pain, sedation, RV dysfunction, and pulmonary status are essential for successful early extubation and good outcomes. Reintubation after extubation failure is associated with increased morbidity, hospital stay and mortality. A factor that might contribute to extubation failure is delirium, a condition that often is treated with additional sedation and sometimes leading to inadequate ventilation [104, 105].

Postoperative care for surgical repair

After chest closure, the patient is prepared for planned immediate extubation after meeting extubation criteria. Otherwise, the patient remains intubated and ventilated while receiving adequate sedation during transport to the ICU. Regardless of whether the patient continues mechanical ventilation or is extubated, analgesia and adequate sedation can be provided with morphine (20–40 μg/kg/hour) and dexmedetomidine (0.3–0.7 μg/kg/hour) infusions at titrated doses.

KEY POINTS: TETRALOGY OF FALLOT

- Decreases in SVR and catecholamine surges can trigger hypercyanotic episodes. Anesthetic induction and periods of surgical manipulation are especially vulnerable times.
- Hypercyanotic episodes are managed with IV fluids, oxygen, phenylephrine, increased anesthetic depth, and knee-chest positioning or abdominal compression.
- During mBTS placement, hypoxemia and hemodynamic instability often occur during the shunt placement. After shunt opening, hypotension with widened pulse pressure occurs.
- Postoperative ventilation is recommended after mBTS placement due to the risk of pulmonary edema and coronary artery ischemia from diastolic hypotension.
- Coronary arteries crossing the RVOT may preclude the option to use a transannular patch repair. A RV to pulmonary artery conduit is an alternative.
- Patients with RV hypertrophy and diastolic dysfunction require high-filling pressures to maintain adequate CO.
- Following full repair, RV dysfunction, tachydysrhythmias, and bleeding should be anticipated.
- Significant residual VSDs result in poorly tolerated excessive PBF.

Pulmonary stenosis with intact ventricular septum

Incidence, anatomy, and natural history

PS/IVS is a fairly common malformation, consisting of 10% of congenital heart defects [2]. The lesion can be further divided into three groups: valvar, subvalvar, or supravalvar. Valvar PS is the most common [80–90% of reported cases of PS] while subvalvar or supravalvar (including stenosis of the BPAs) varieties are less common [106]. Acuity can range from asymptomatic (mild valvar PS) to requiring urgent intervention (ductal-dependent or "critical" PS).

The stenotic pulmonary valve may be unicuspid, bicuspid, or tricuspid and is dome-shaped or dysplastic with a narrow, central opening. Obstruction to the RVOT may lead to hypertrophy of the infundibulum, eventually leading to diastolic dysfunction as ventricular compliance worsens [107]. Valvar PS is commonly associated with other defects such as Noonan syndrome, ASD, EA, double outlet RV, and transposition of the great arteries [108].

Subvalvar PS can be divided into two further subtypes: infundibular and subinfundibular. Infundibular PS is usually a part of TOF whereas subinfundibular PS occurs within the context of double-chambered RV (DCRV). A DCRV is caused by an anomalous muscle band that runs between the anterior wall to the ventricular septum [109]. These muscle bands divide the RV cavity into a proximal high-pressure chamber and a distal low-pressure chamber that if not surgically corrected, may progressively worsen and lead to DCRV. Supravalvar PS is seen in many disorders such as congenital rubella, Williams, Noonan, Alagille, DiGeorge, and Leopard syndromes [108] (Table 28.8). The stenosis can be localized to the MPA, as well as the bifurcation, and/or the BPAs proper. If the stenosis is located in the MPA, there is usually poststenotic dilation of the MPA and sometimes of the LPA as well.

Pathophysiology

Newborns with critical PS may present with heart failure that results from suprasystemic RV pressure, significant TR and right-to-left shunting via an ASD or PFO. However, most patients have mild to moderate PS and are asymptomatic at birth, developing symptoms gradually. Many patients are initially discovered by the presence of a systolic ejection murmur on routine physical exam. Individuals with mild to moderate PS have been documented to survive well into their 4th decade of life [108]. Symptomatically, patients present with dyspnea, fatigue, and sometimes syncope. Patients with mild PS may have a normal ECG, whereas an ECG in a patient with severe stenosis may show right axis deviation and evidence of RV hypertrophy. Echocardiography with Doppler evaluation can be used to grade peak and mean gradients, location of the stenosis, presence of DCRV, and with the advent of 3D echocardiography, accurately estimate RV volume and ejection [110]. MRI can be used to study anatomy and establish the exact location of the stenosis (supravalvar, valvar, or subvalvar) as well as decrease exposure to ionizing radiation, as with multislice computed tomography (CT) scans. Limiting factors for MRI imaging include

Table 28.8 Common genetic syndromes associated with pulmonary stenosis [108]

Syndrome	Genetic defect	Cardiac features	Non-cardiac features
Noonan	PTPN11, SOS1, aberrant RAS-MAPK-signaling, heterogenous trait	Dysplastic pulmonary valve stenosis, hypertrophic cardiomyopathy	Short stature, hypertelorism, downward eye slant, low set ears
Williams-Beuren	7Q11.23 deletions, autosomal dominant trait	Supravalvular aortic or pulmonary stenosis	Elfin face, short stature, impaired cognition and development, endocrine disorders, genitourinary abnormalities
Leopard	PTPN11, RAF-1, autosomal dominant trait	Electrocardiographic abnormalities, supravalvular or valvular pulmonary stenosis	Lentigines, ocular hypertelorism, abnormal genitalia, retardation of growth, deafness
DiGeorge (velocardiofacial)	22Q11 deletion, autosomal dominant trait	Conotruncal defects such as tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, vascular rings and ASD/VSD	Hypertelorism, low set and posteriorly rotated ears, palatal abnormalities, micrognathia, developmental delay, hypoplastic thymus, hypocalcemia, variety of immunological abnormalities
Alagille	JAG-1, NOTCH-2, dominant trait	Peripheral pulmonary stenosis	Facial dysmorphias (triangular face, wide nasal bridge, deep set eyes), intrahepatic cholestasis, butterfly vertebrae
Keutel	MGP mutations, autosomal recessive trait	Multiple peripheral pulmonary stenoses	Abnormal cartilage calcifications, brachytelephalangy, subnormal IQ, hearing loss
Congenital rubella	–	Peripheral pulmonary stenosis, open ductus Botalli	Congenital cataract/glaucoma, deafness, pigmentary retinopathy

ASD, atrial septal defect; VSD, ventricular septal defect.

incompatibility with pacemakers and requirements for breath holds. Cardiac catheterization is utilized diagnostically to directly measure pressure gradients and evaluate anatomy via angiography but is used primarily for interventional options such as balloon valvuloplasty.

Surgical and transcatheter approaches and outcomes

Transcatheter balloon valvuloplasty is now considered the first-line treatment for PS. The procedure is considered when patients exhibit symptoms, have a PV mean gradient greater than 40 mmHg while sedated, or have clinically significant PS with RV dysfunction on echocardiography [108]. Exceptions include cases involving a hypoplastic annulus, severely dysplastic valve, and other associated congenital cardiac lesions. In these cases, surgery may be the preferred initial option [108]. Percutaneous balloon valvuloplasty can be used serially for PV stenosis that recurs over time and is considered successful when the mean gradient is reduced to less than 30 mmHg. The incidence of PI after balloon valvuloplasty is 80%, but it is usually mild in clinical severity. In the past, postprocedural PI was noted with little concern, but correlations between long-standing PI, RV dilation, and potential decreases in RV function have led some centers to utilize smaller balloons and tolerate some residual PS [107]. Complications, though rare, include transient bradycardia and hypotension with balloon inflation, transient/permanent AV block, tricuspid papillary muscle rupture and MPA rupture. However, with experienced providers, the risk of death/major complications is exceedingly low (0.24%/0.35%, respectively). Beta-blockers may be needed infrequently to reduce contractility in a hyperdynamic RV after valvuloplasty.

If balloon valvuloplasty fails, or if there are more complicated lesions (usually sub- or supravalvar stenosis), surgical repair with CPB may be necessary. For valvar stenosis, open commissurotomy or valvulotomy is usually performed through a vertical incision in the pulmonary trunk. If necessary, a transannular patch of autologous pericardium can be placed. Subvalvar obstruction in the infundibular region can be excised and an MPA patch placed. If valve replacement is required (as in the case of severe postprocedural PI), implantation of a bioprosthetic valve is preferred as the risk of thrombosis in pulmonary mechanical valves is higher than in mechanical valves in the aortic position [108]. Pulmonary homograft or other bioprosthetic valves may be used. Patients with prior valve replacements that have developed stenosis or regurgitation can be candidates for percutaneous valve implantation.

Despite successful pulmonary balloon valvuloplasty, some neonates with critical PS may exhibit cyanosis with ductal closure, and a PGE_1 infusion will need to be reinstated. As RV hypertrophy diminishes and RV compliance improves, PGE_1 may be weaned. If the neonate remains ductal-dependent for PBF after 2–3 weeks, a systemic-to-pulmonary arterial shunt or PDA stent may be required. About 15–20% of neonates with critical PS will eventually need surgical intervention.

Anesthetic considerations

Periprocedural anesthesia for transcatheter pulmonary balloon valvuloplasty

Neonates with critical PS require PGE_1 to maintain adequate PBF and urgently undergo PV transcatheter intervention. Often, these infants are supported prior to the

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procedure with mechanical ventilation and inotropic support. Anesthetic agents may include inhalational agents supplemented with low-dose opioids and muscle relaxants. Procedural stimulation is limited beyond establishment of venous access for catheterization, so anesthetic requirements are minimal. Intraprocedural complications include temporary bradycardia and hypotension during balloon inflation and transient AV block. After sufficient PV dilation, an immediate reduction in the transvalvar gradient is observed with angiographic evidence of increased PBF. At the time of the sudden relief of PV obstruction, filling pressures will require immediate support with the administration of intravascular volume such as 5% albumin in order to maintain forward flow from the hypertrophic, low-compliance RV. After establishing PBF through the PV, PGE_1 is discontinued. The neonate returns to the ICU with mechanical ventilation for adjustments of inotropic support and ventilation.

Older infants and children with PS usually present electively for pulmonary balloon valvuloplasty. Inhalational anesthetic induction followed by establishment of intravenous access is generally well-tolerated. The intraprocedural complications are similar to those above. Maintenance of anesthesia can be accomplished with inhaled anesthetic agents supplemented with low-dose opioids as necessary. After successful pulmonary balloon valvuloplasty, some patients may have transient dynamic RVOTO secondary to infundibular hypertrophy. A beta-blocker such as with an infusion of esmolol can reduce contractility and heart rate. Increasing right heart filling pressures with intravascular volume administration assists in enhancing right heart CO by increasing preload and overcoming RVOTO. After balloon valvuloplasty of severe PS, the sudden enhancement of PBF can result in reperfusion pulmonary edema, requiring adjustments of mechanical ventilation and especially PEEP. In most cases, the intraoperative course is uneventful, and the patient can be extubated at the conclusion of the catheterization procedure. Local anesthetic infiltration of the access sites, titration of dexmedetomidine for post-procedural sedation and acetaminophen analgesia are usually sufficient for a smooth anesthetic emergence and recovery.

Perioperative anesthesia for surgical valvotomy

Preoperative

In the current era of transcatheter interventions, surgical valvotomy is reserved for those patients that have failed the transcatheter approach or have multilevel fixed RVOTO not amenable to transcatheter intervention. Patients are medically optimized prior to surgery, particularly those with PS complicated with CHF.

Intraoperative

Premedication, anesthetic induction, and intubation are tailored to the clinical status of the patient. Anesthetic management prior to CPB is directed towards preservation of ventricular function and optimization of PBF. Anesthetic induction can be accomplished with low-dose fentanyl, with or without ketamine (depending on the presence of dynamic RVOTO), and low levels of anesthetic agent such as sevoflurane. Meticulous titration of inhaled anesthetic agent with sufficient muscle relaxation and opioid infusion is appropriate for anesthetic maintenance. Continuous arterial blood pressure monitoring with central venous access for central venous blood pressure monitoring and drug administration are established prior to surgery. Cerebral and somatic NIRS monitoring for regional tissue oxygenation and TEE for assessment of the RVOT status and cardiac function are useful.

After completion of the surgical valvotomy, a milrinone infusion can be used to facilitate RV relaxation and lower PVR. Generous RV preload will be necessary to accommodate a noncompliant hypertrophic RV. As the patient is weaned from CPB, the sudden increase in PBF can result in reperfusion pulmonary edema. Mechanical ventilation with sufficient PEEP will be required to maintain airway gas exchange. Transient RV dysfunction, especially after a right ventriculotomy approach, may require inotropic support such as with low-dose epinephrine. Excessive inotropy can be detrimental if residual dynamic RVOTO is present. For a hyperdynamic RV, CO may actually be improved with an esmolol infusion by reducing dynamic RVOTO. Commonly, a residual pressure gradient with persist across the RVOT after surgical repair, improving over the first 24 postoperative hours.

Postoperative

If reperfusion pulmonary edema is evident or suspected, patients are best managed with postoperative mechanical ventilation with sufficient PEEP until the pulmonary vasculature has accommodated the increased PBF. Residual infundibular hypertrophy usually resolves over time with removal of the valvar obstruction. Effective postoperative analgesia and sedation are accomplished with opioid and dexmedetomidine infusions as well as IV acetaminophen. Early extubation is reserved for patients with mild PS, an uneventful intraoperative course, adequate ventricular function, and no evidence of reperfusion pulmonary edema.

KEY POINTS: PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

- Valvar PS is most common at 80–90% of cases, with subvalvular and supravalvular types making up the remaining 10–20%.
- Successful percutaneous balloon valvuloplasty results in a transvalvar gradient of less than 30 mmHg.
- Beta-blockers may be useful in reducing contractility in a hyperdynamic RV after percutaneous balloon valvuloplasty.
- In the immediate period after repair, RV filling pressures must be adequate while avoiding high pulmonary artery pressures; adequate RV preload and pulmonary vasodilators are useful treatments.

Pulmonary atresia with intact ventricular septum

Incidence, anatomy, and natural history

PA/IVS is a rare (accounting for 3% of congenital heart defects) right heart obstructive lesion defined by the presence of an atretic PV and an IVS (absence of a VSD). Males are more likely to have PA/IVS with a male to female ratio of 1.5:1 [111]. Although the etiology of the defect is unknown, there is evidence to suggest that atresia of the PV may be a result of abnormal coronary arterial development [112]. Patients commonly develop TR or coronary fistulas in an effort to help decompress the hypertensive RV [113]. Typically, there is a PFO or secundum ASD that is restrictive in 5–10%. The TV is generally smaller than normal but can range from extremely stenotic to the dilated annulus of EA (5–10%). The RA is dilated proportionately to the degree of TR. The RV is hypertrophic with a reduced cavity. In about 50% of cases, there are endothelial-lined blind channels within the RV myocardium known as sinusoids that may be remnants of vessels providing nutrients to the ventricles prior to the formation of coronary arteries. Sinusoids are in direct communication with the RV cavity and sometimes to the coronary arteries, becoming RV to coronary artery fistulae. Sinusoids may persist due to RV hypertension. In the least affected individuals, RV blood is sent as part of a dual blood supply to small areas of myocardium in tandem with normal aortocoronary flow. But approximately 20% of patients with PA/IVS have an absence of anterograde aortocoronary flow, a finding confirmed with either cardiac catheterization or computed tomography (Figure 28.20). In this circumstance, the coronary bed is perfused with poorly saturated systemic venous blood directly from the RV and the RV myocardium is chronically ischemic. In the most severely affected, aortocoronary connections will be absent and coronary cameral connections with the RV establish an RV-dependent coronary circulation (RVDCC) that supplies the RV myocardium [113].

Sometimes the PV appears intact, but with fused commissures. Most often, there is fibrous tissue at the ventriculoarterial junction. The pulmonary arteries usually have normal branching and can be hypoplastic in about 6% of cases. There is almost always a PDA. The LA is enlarged and hypertrophic. Subaortic stenosis can result from bulging of the ventricular septum into the LV due to RV hypertension.

Without treatment, PA/IVS results in death in 50% of neonates, and in 85% of infants by 6 months of age. Fetuses with small, hypertrophied ventricles often survive to birth, whereas those with dilated RVs and severe TR may die in utero with fetal hydrops. Postnatal death is usually due to hypoxemia which is exacerbated by closure of the ductus arteriosus, and eventual myocardial ischemia and infarction [114].

Pathophysiology

Many fetuses with PA/IVS succumb to intrauterine demise or develop hydrops fetalis from RV failure, but for some surviving neonates who have not developed hydrops fetalis, moderate TR may have allowed the RV pressure to remain low such that sinusoids and coronary fistulae have not developed. Alternatively, if TR is mild or the valve is competent, the neonatal RV will be small and hypertrophic with marked systolic hypertension. This subset, with a competent or nearly competent TV and suprasystemic RV pressure, is at higher risk for coronary artery abnormalities such as coronary cameral connections with the RV, coronary ostial stenosis and atresia, and absent aortocoronary connections. Coronary cameral connections with the RV, or RVDCC, perfuse the RV myocardium with blood at oxygen levels and pressures of the RV. The RVDCC are dependent on

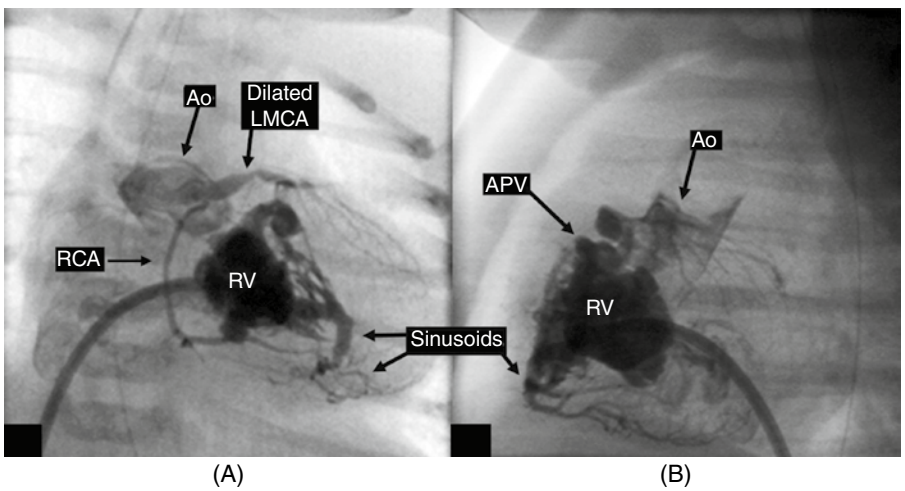


Figure 28.20 Pulmonary atresia with intact ventricular septum in a 1-day-old infant. A National Institutes of Health (NIH) catheter has been placed prograde into the right ventricle (RV) via a hypoplastic tricuspid valve for a contrast hand injection. There is mild tricuspid regurgitation. Numerous coronary sinusoids from the RV cavity to both right coronary artery (RCA) and left coronary artery are demonstrated. Contrast faintly opacifies the aorta (Ao) retrograde through a dilated left main coronary artery (LMCA). (A) Frontal view. (B) Lateral view. RV outflow tract ends at the atretic pulmonary valve (APV). (Source: Schmitz et al. [38]. Reproduced with permission of John Wiley & Sons.)

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RV pressures while in turn, adequate RV pressure generation is reliant on myocardial perfusion/oxygenation by the RVDCC. Patients with RVDCC are at an elevated risk for myocardial ischemia and infarction, particularly if the high-pressure RV becomes decompressed. RV decompression allows diastolic runoff from the aorta through the coronaries into the RV chamber at lower pressures, thereby creating coronary "steal" with resulting myocardial ischemia. RVDCC is present in 9–34% of patients with PA/IVS [115]. In addition, LV hypertrophy and dilation, and possible aortic root dilation may be present due to increased left heart flow across the foramen ovale in utero.

After birth, the PDA remains the sole source of PBF, and early initiation of PGE_1 is key for survival to surgical repair or palliation. An atrial communication is necessary for right-to-left shunting of systemic venous return, mixing on the left side of the heart with oxygenated blood from the pulmonary veins. The newborn with PA/IVS demonstrates functional single ventricle physiology so that the distribution of systemic and PBF is dependent on PVR/SVR ratios. Thus, arterial saturation is principally obtained by three variables: Qp:Qs, systemic venous saturation, and pulmonary venous saturation.

The ECG reveals small RV forces and often a tall P wave, indicative of RA enlargement. The chest radiograph often shows decreased to normal pulmonary vascular markings depending on the amount of ductal flow. The cardiac silhouette is normal unless RA and RV enlargement occur due to severe TR. Echocardiography can define the atrial septum (adequacy of atrial communication), TV (size, function, and morphology), RV (evidence of hypertrophy and functional structure), RVOT (membranous vs muscular PA) and PDA (size and direction of blood flow). While proximal coronary artery anatomy and the presence of coronary cameral connections can be delineated by echocardiography, cardiac catheterization or computed tomography may be necessary to adequately visualize coronary artery abnormalities, with cardiac catheterization being the preferred tool to concurrently provide therapeutic interventions [116].

Surgical and transcatheter approaches and outcomes

In the early 1960s, palliative shunts and closed pulmonary valvotomies were done. However, survival was dismal given that an estimated 2.5% of patients survived to 3 years of age. CPB-assisted RV outflow procedures were combined with systemic-to-pulmonary arterial shunts in the 1970s. Since that time the therapeutic approach has been directed toward the following outcomes: biventricular circulation, single ventricle (including 1.5 ventricle) palliation, or cardiac transplantation, depending on RV size and anatomy (unipartite, bipartite, or tripartite), TV and PV size, subPV stenosis, TR, ventriculocoronary connections, and RVDCC [113] (Figure 28.21).

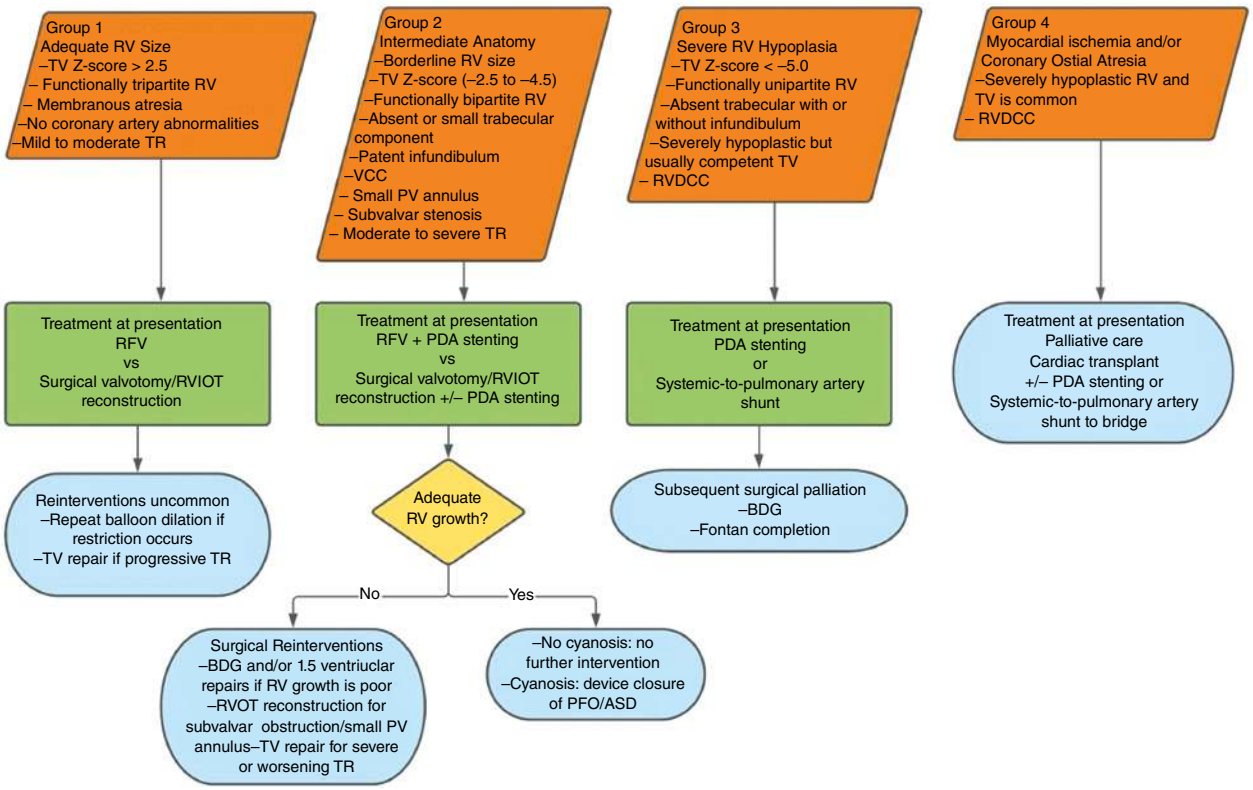


Figure 28.21 Strategies for the management of variants of pulmonary atresia with intact ventricular septums from Chikkabyrappa et al. [113]. ASD, atrial septal defect; BDG, bidirectional Glenn; PDA, patient ductus arteriosus; PFO, patent foramen ovale; PV, pulmonary valve; RFV, radiofrequency valvotomy and balloon dilation; RV, right ventricle; RVDCC, right ventricle-dependent coronary circulation; RVOT, right ventricular outflow tract; TR, tricuspid regurgitation; TV, tricuspid valve; VCC, ventriculocoronary connections. (Source: Michael L. Schmitz, MD.)

Patients with PA/IVS are usually first evaluated via cardiac catheterization with hemodynamic measurements, coronary angiography, and possible intervention. Once the absence of RVDCC is confirmed, decompression of the RV via percutaneous pulmonary valvotomy with radiofrequency ablation, wire or laser and balloon dilation can be undertaken. Other interventions may include balloon atrial septostomy and balloon dilation or stenting the PDA.

Initial neonatal surgical options include:

- RVOT reconstruction with surgical valvotomy
- RVOT reconstruction with surgical valvotomy and PDA stenting
- Systemic-to-pulmonary arterial shunt
- Cardiac transplant or systemic-to-pulmonary arterial shunt as bridge to transplant

After the initial neonatal palliation, the decision about subsequent procedures and a biventricular repair vs. single ventricle palliation depends on similar initial considerations such as RV and TV size and function [113, 117, 118] (Figure 28.21). To evaluate for biventricular repair, oxygen saturations and potential for further RV growth are assessed. Within 6 months after the initial procedure, the systemic-to-pulmonary artery shunt and the ASD can be temporarily occluded in the cardiac catheterization laboratory. If oxygen saturations remain appropriate and the right atrial pressure remains below 12–15 mmHg with adequate CO, the patient may be a candidate for biventricular repair [119].

If biventricular repair is not feasible, the patient proceeds to a BDG. Patients with inadequate RV size retain an open ASD and proceed to Fontan palliation. Those who have intermediate RV size and some degree of RV outflow might proceed to a BDG with ASD closure, resulting in a 1.5 ventricle palliation. If tolerated, a 1.5 ventricle palliation may be preferable to a Fontan circulation as it may lead to a step-down in pressure in the IVC and a step-up in pulmonary artery pressures, avoiding the caval hypertension and potential pulmonary arterial hypotension with a Fontan circulation [118].

Surgical options for PA/IVS with RVDCC are more limited as procedures are limited to those that do not decompress the obstructed RV. Initial options include placement of a systemic-to-pulmonary artery shunt or ductal stent to provide a stable source of PBF with the ultimate goal of single ventricle palliation or cardiac transplant. As mortality exceeds 50% in infancy for patients undergoing single ventricle palliation, cardiac transplant may be a more viable option [115].

As Reddy and Hanley [120] stated more than two decades ago, the goals of initial surgical intervention for neonates with inadequate RV anatomy are to:

- Minimize mortality
- Promote growth of the RV to improve chances for a subsequent two ventricle repair
- Minimize the requirement for later non-definitive surgical intervention

The systemic-to-pulmonary artery shunt can be a non-defining initial palliation with relatively low mortality and for neonates with small RVs without RVDCC and allowing the RV to decompress may allow for RV growth. The systemic-to-pulmonary artery shunt allows time to later estimate the ultimate functional potential of the RV, potential that is often unclear in neonatal PA/IVS.

Anesthetic considerations

Despite the multitude of interventional and surgical options available for PS/IVS and PA/IVS, there are some general considerations for perioperative care [118] (Table 28.9).

Table 28.9 Key considerations in the perioperative management of pulmonary atresia with intact ventricular septum (PA/IVS)

Perioperative period	Key considerations

Preoperative	• Neonates dependent on PGE_1
	  ○ Appropriate physiologic monitoring
	  ○ Stable vascular access
	• Standard preoperative evaluation:
	  ○ ECG
	  ○ TTE
	  ○ Chest X-ray
	  ○ Cardiac catheterization (to evaluate coronary anatomy and identify RVDCC

Intraoperative	• Neonatal palliation
	  ○ Systemic-pulmonary artery shunt
	  ■ Balance Qp:Qs
	  ■ Avoid diastolic blood pressure hypotension
	  ■ Monitor ECG closely for signs of myocardial ischemia
	  ○ RV decompression procedure (valvotomy or transannular patch)
	  ■ Maintain RV preload/filling pressure
	  ■ RV inotropic support
	  – Milrinone
	  – Dobutamine/epinephrine
	  – Nitric oxide to reduce RV afterload
	• 2nd Stage BDCPA or 1.5-ventricle palliation
	  ○ Adequate preload delivery to partially unloaded RV
	  ○ Avoid high PVR
	  ○ Mild hypercarbia post-BDCPA
	  ○ Adequate oxygenation
	• 3rd Stage Fontan circulation
	  ○ Maintain intravascular volume
	  ○ Ensure atrioventricular synchrony (sinus rhythm or AV pacing)
	• RVDCC (10% of PA/IVS patients)
	  ○ Cannot undergo procedure to decompress the obstructed RV
	  ○ Maintain RV pressures and avoid decompression
	  ○ CPB cases: second arterial cannula via the RA used to pressurize the RV
	  ○ Partial CPB flow with mechanical ventilation (reported option)

Postoperative	• Early extubation
	  ○ Negative intrathoracic pressure reduces RV afterload and increases PBF
	  ○ RV inotropic support

BDCPA, bidirectional cavopulmonary anastomosis; CPB, cardiopulmonary bypass; ECG, electrocardiogram; PA, pulmonary artery; PBF, pulmonary blood flow; PGE_1, prostaglandin E_1; PVR, pulmonary vascular resistance; Qp:Qs, pulmonary:systemic blood flow; RV, right ventricle; RVDCC, right ventricular-dependent coronary circulation; TTE, transthoracic echocardiogram.

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Postnatal TTE results can help guide anesthetic planning. If RV fistulas are a concern, maintenance of RV preload and systemic diastolic pressure are essential to preserve coronary perfusion pressure [118]. Risks involving cardiac catheterization should be anticipated, including difficulty with obtaining vascular access, injury to large vessels and myocardium, and hemorrhage.

Neonatal palliation

Neonates with PA/IVS may undergo systemic to pulmonary arterial shunt in isolation or combined with pulmonary valvotomy. (Patients with RVDCC will be discussed separately below.) Procedures may be performed with or without CPB via a sternotomy or thoracotomy. Monitoring should include arterial and central venous line access, NIRS, and TEE. Anesthetic induction and maintenance are performed with a combination of opioid, inhaled anesthetic agent and muscle relaxant. Careful consideration should be given to maintaining an appropriate Qp:Qs balance and diastolic BP to provide adequate CO and avoid myocardial ischemia respectively. For any patient with a small hypertrophic, hypertensive RV, RV filling pressures must be maintained such that the RV cavity does not collapse, and thus maintain CO. For patients undergoing RV decompression on CPB, preservation of filling pressures is essential as poor RV preload will compromise CO. This is particularly important in patients undergoing repairs leading to biventricular circulation. Inotropic RV support is often needed as RV dysfunction is commonly present after CPB. Optimizing ventilation pressures and utilizing pulmonary vasodilators with drugs such as milrinone (0.375–0.75 μg/kg/min) help to reduce RV afterload. If pulmonary hypertension was present prior to repair, iNO can be used to aid in pulmonary vasodilation until the vascular bed adjusts to the increased flow. Postoperatively, expedited tracheal extubation and resumption of spontaneous ventilation aid in improving PBF and reducing RV afterload. Narcotic infusions to ensure adequate analgesia will reduce oxygen demands from agitation.

For a few patients who undergo systemic-to-pulmonary artery shunt placement, low CO in the postoperative period could be caused by either unrecognized RVDCC or from a "circular shunt" (described earlier in this chapter). A circular shunt arises in patients who have had both a pulmonary valvotomy and a systemic-to-pulmonary arterial shunt and have significant PI. In this situation, blood ejected from the LV flows through the systemic-to-pulmonary arterial shunt and to the pulmonary circulation. Due to PV incompetence, blood proceeds retrograde along a declining pressure gradient to the RV, and depending on the competence of the TV, into the RA, and then the LA via the interatrial communication. The "steal" of blood from the systemic circulation causes systemic hypoperfusion with resulting metabolic acidosis. Raising the PVR and reducing the SVR may be helpful in improving systemic perfusion, but surgery is often needed to revise the shunt and treat TR.

Single ventricle palliation (including 1.5 ventricle palliation and Fontan procedure)

On initial presentation, infants unable to undergo biventricular repair (primarily those with severe RV/TV hypoplasia and/or RVDCC) instead have stabilization of their PBF by various mechanisms. With borderline RV size, PBF can be enhanced and stabilized by radiofrequency pulmonary valvotomy with PDA stenting, surgical pulmonary valvotomy and RVOT reconstruction with or without PDA stenting, or in the case of severe RV hypoplasia, PDA stenting or systemic-to-pulmonary artery shunt placement [113]. Monitoring is similar to that of neonatal palliation with care to place the arterial line monitoring on the contralateral side of systemic-to-pulmonary shunts utilizing innominate or subclavian arteries. For subsequent establishment of a bidirectional cavopulmonary anastomosis (BDCPA), central venous access is often placed in the right or left internal jugular vein to measure superior cavopulmonary pressure. For initial procedures on infants to stabilize PBF, the induction and maintenance of anesthesia is also similar to PS/IVS and performed via a combination of opioids, inhaled anesthetic agent, and muscle relaxants. For construction of the BDCPA, hyper- or hypocapnia and hypoxia are avoided and low PVR is maintained to provide adequate PBF. Early extubation and postoperative positioning with the upper body elevated 30 degrees can improve facilitate PBF. Intraoperative considerations for 1.5 ventricle palliation are similar to that of the single-ventricle BDCPA with the caveat that the small RV will be very dependent on preload and require inotropic support including milrinone as described above. For a later Fontan procedure, anesthetic goals include early extubation with upper body elevation, maintenance of intravascular volume, adequate sedation and analgesia (e.g., dexmedetomidine and narcotic infusions as described previously) to reduce oxygen demands, and AV synchrony (sinus rhythm or AV pacing) and discussed in detail elsewhere in this volume.

RVDCC

Patients with RVDCC are tenuous from a hemodynamic standpoint and require constant communication with the surgical and perfusion teams for optimal care [118]. For procedures requiring CPB (including those mentioned above), RV pressure can be maintained through a second arterial cannula placed transmurally into the RA and secured with a purse string suture. Alternatively, partial CPB with continued mechanical ventilation can be employed to maintain RA pressure [115]. As mentioned previously, strategies to prevent RV decompression are critical in patients with RVDCC as it may lead to severe ischemia and death if not employed.

KEY POINTS: PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

- Approximately 20% of patients with PA/IVS do not have anterograde aortocoronary flow and have a chronically ischemic myocardium with RVDCC.
- Mortality in untreated infants is 50% by 1 month and 85% by 6 months of age.
- For any patient with a small, hypertrophic, hypertensive RV, filling pressures must be maintained to prevent RV collapse.
- Filling and RV pressure must be maintained for patients with RVDCC at all times to prevent "coronary steal" from the myocardium, even while on CPB.

Pulmonary atresia/ventriculoseptal defect/major aortopulmonary collateral arteries

Incidence, anatomy, and natural history

PA/VSD/MAPCAs or TOF/PA is a rare defect that involves features of TOF (infundibular hypertrophy, large misaligned VSD) with a lack of continuity between the RV and pulmonary trunk and varying levels of pulmonary arterial hypoplasia, thus causing heterogeneity in regards to PBF. The incidence is 0.7 per 10,000 live births for PA/VSD/MAPCAs [121]. The native MPA and BPAs are absent in 20–25% of patients, with significant abnormalities in the remaining 75–80% that do have intrapericardial native BPAs [122]. In the latter group, native BPAs are inevitably hypoplastic to varying degrees, likely due to lack of antegrade flow from the RV and retrograde flow from MAPCAs [123]. Lung parenchyma may be perfused singly by native BPAs or MAPCA flow, or redundantly by both. MAPCAS vary in number, size, and origin with the most common origin being the descending thoracic aorta, but not infrequently involving the innominate, subclavian, internal mammary, and coronary arteries as well, and usually traverse through the posterior mediastinum associating with the major airways and at times the esophagus [123]. Unfortunately, MAPCAs commonly develop stenosis at the point of their origin, causing the area supplied by the MAPCA to become underperfused without an alternate source of PBF. A classification system has been proposed, based on the morphology of the pulmonary arteries and MAPCAs, that can be useful for surgical decisions [124] (Figure 28.22). Of note chromosome 22q11 deletion may be present in >35% of patients with TOF/PA/MAPCAs [125].

Disease progression of TOF/PA is best done by organizing patients into three distinct groups based on PBF, each of which has differing mortality outcomes. The first group has a PDA as the source of PBF, and more than 50% die by 6 months of age and 90% by 1 year. In the second group MAPCAs are present with a PDA as PBF; 50% die by 3–5 years of age and 90% within 10 years. In the third group, multiple and large MAPCAs are present as the only source of PBF. In this group, only mild cyanosis may present on physical exam, without signs of CHF; when left untreated, patients usually live into the third decade, but eventually die from pulmonary vascular disease resulting in Eisenmenger syndrome [126].

Pathophysiology

TOF/PA can be viewed as a mixed lesion with PBF determined by overall TR with highly variable sources of PBF. Approximately 90% of patients have nearly balanced Qp:Qs, with oxygen saturations between 75–90% while the remaining 10% present with either excess (O2 saturation >90%) or decreased (O2 saturation <75%) PBF leading to pulmonary congestion/CHF or metabolic acidosis respectively [123]. It is important to note that MAPCA patency is dynamic as proximal stenosis of the vessels is common and leads to ischemic loss of lung segments.

Fetal and neonatal echocardiography is useful to identify PA and presence of a VSD and MAPCAs; however, virtually all patients require cardiac catheterization and/or CT/MRI angiography to fully delineate the pulmonary artery and collateral artery anatomy and determine the appropriate surgical approach (Table 28.10). MRI or CT with three-dimensional reconstruction of the images is also useful in outlining

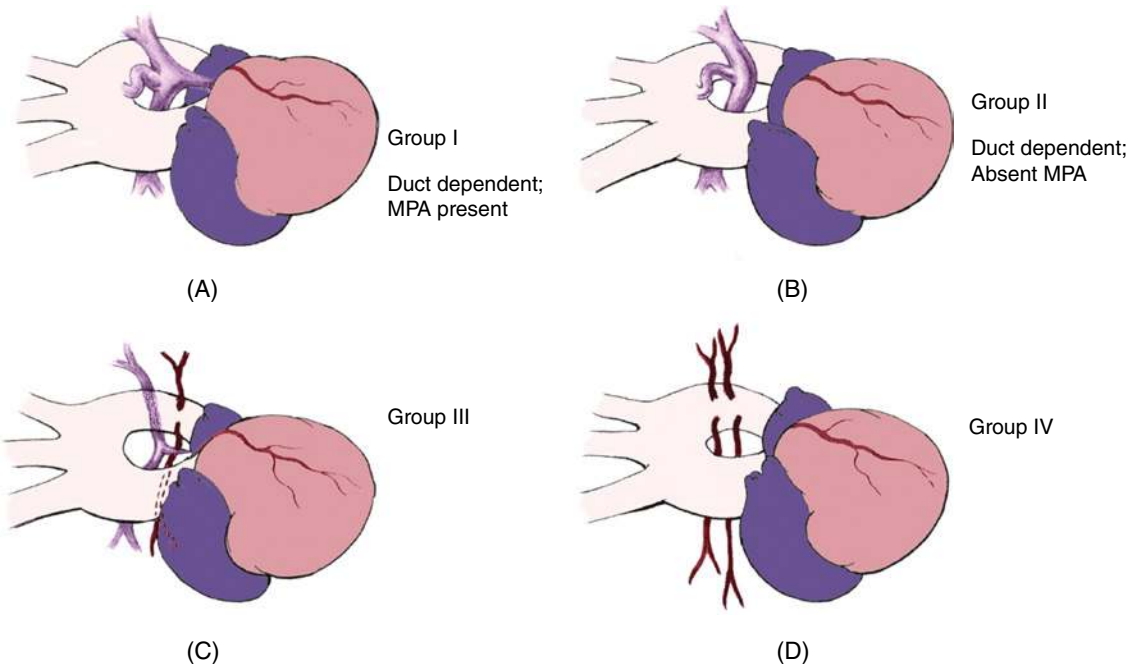


Figure 28.22 Tetralogy of Fallot with pulmonary atresia occurs with much variation depending on the development of the true pulmonary arteries and aortopulmonary collateral arteries. (A) Group I: simple valvular or infundibular atresia. (B) Group II: ductal-dependent branch pulmonary arteries and absence of the main pulmonary artery (MPA). (C) Group III: hypoplastic true pulmonary arteries with major aortopulmonary collateral arteries. (D) Group IV: true pulmonary arteries are absent, and all pulmonary blood supply is from major aortopulmonary collateral arteries. (Source: Jonas [124]. Reproduced with permission of Taylor & Francis.)

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Table 28.10 Factors contributing to the surgical plan for pulmonary atresia/ventricular septal defect/major aortopulmonary collateral arteries

- Size and morphology of the native pulmonary arteries
- Branching of the native pulmonary vasculature
- Quantity of pulmonary blood flow from all sources
- Age of the patient

complex anatomy (Figure 28.23). Three dimensional CT often is the better option for the fine resolution needed for infants (Figure 28.24).

Surgical and transcatheter approaches and outcomes

Ma et al. [123] note the approach to surgical repair is threefold:

1. Achieve normal physiology and biventricular repair by minimizing TR with preservation and augmentation of the PBF, usually accomplished via early/complete unifocalization if needed. (see later in section for description of unifocalization procedure).
2. Complete biventricular repair with atrial and VSD closure with placement of an RV to pulmonary artery valved conduit in patients with a RV systolic pressure that is 50% or less of the LV systolic pressure: Patients not meeting this pressure ratio receive a central shunt, and intracardiac repair is delayed until a RV/LV pressure ratio of 0.5 is achieved in follow-up cardiac catheterization.
3. Periodic surveillance with indicated studies (CTA/MRI/cardiac catheterization) to assess the adequacy of PBF and decreases in PVR: Post repair, elective balloon angioplasty of recruited MAPCAs and pulmonary arteries as well as embolization of redundant MAPCAs can non-surgically augment PBF (Figure 28.25).

Most patients (85%) are repaired at 3–6 months of age after further maturation of the trachea and secondary airways, decreasing postoperative pulmonary morbidity [127]. The remaining 15% of patients undergo repair in the neonatal period due to the following:

- Unilateral lung perfusion by MAPCAs with contralateral lung perfusion by a PDA: The ductus can close in the neonatal period resulting in loss of ductal-perfused lung. Unifocalization and intracardiac repair is performed with favorable MAPCAs, otherwise a ductal stent or surgical shunt to the ductal-dependent lung is placed. The patient is then repaired later in infancy [128].
- Normally arborized hypoplastic native pulmonary arteries (all lung segments supplied by native BPAs) with redundant blood flow by MAPCAs. MAPCAs are ligated in this situation, and an aortopulmonary anastomosis (Melbourne shunt) can be placed to encourage further pulmonary vascular bed growth [128].

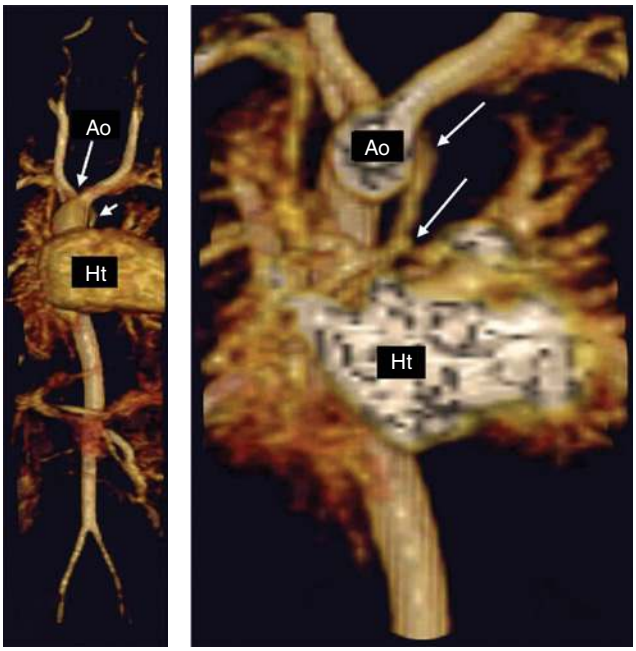


Figure 28.23 Gadolinium-enhanced magnetic resonance angiogram of a 3-day-old, 2.5-kg infant with tetralogy of Fallot, pulmonary atresia, and multiple aortopulmonary collateral arteries. (A) Anterior-posterior view demonstrating a right aortic arch (Ao) and no visible pulmonary artery originating from the heart (Ht). The short arrow shows a large collateral artery originating from the left side of the aortic arch. (B) Same view as the left image, but with the ascending aorta removed. The upper arrow shows the same large collateral artery as seen in the left image descending to supply tiny branch pulmonary arteries (lower arrow). (Source: Schmitz et al. [38]. Reproduced with permission of John Wiley & Sons.)

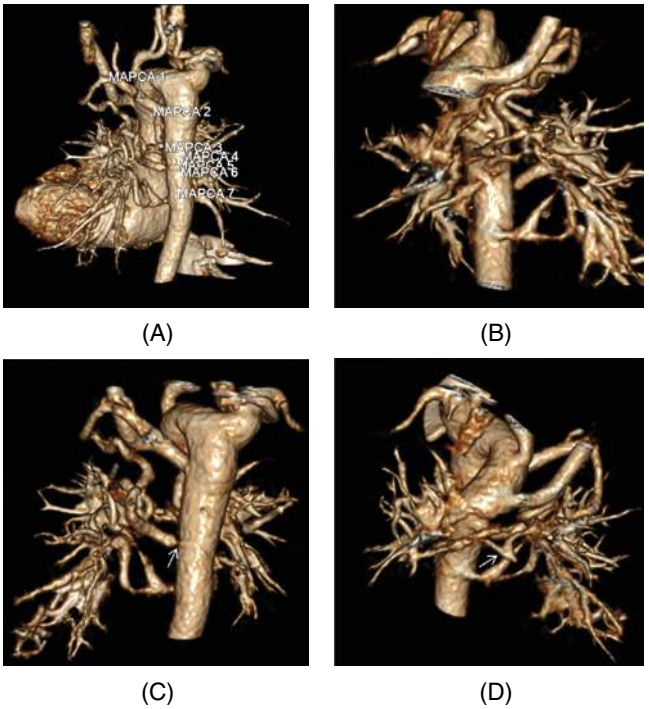


Figure 28.24 Three-dimensional reconstruction of cardiovascular computed tomography scan of a patient with seven major aortopulmonary collateral arteries (MAPCAs). The posterior (A) and anterior (B) views show numerous MAPCAs supplying the lung fields. Proximal stenoses as seen in MAPCA 5 (C, arrow) are common. This patient had severely hypoplastic but confluent native pulmonary arteries (D, arrow).

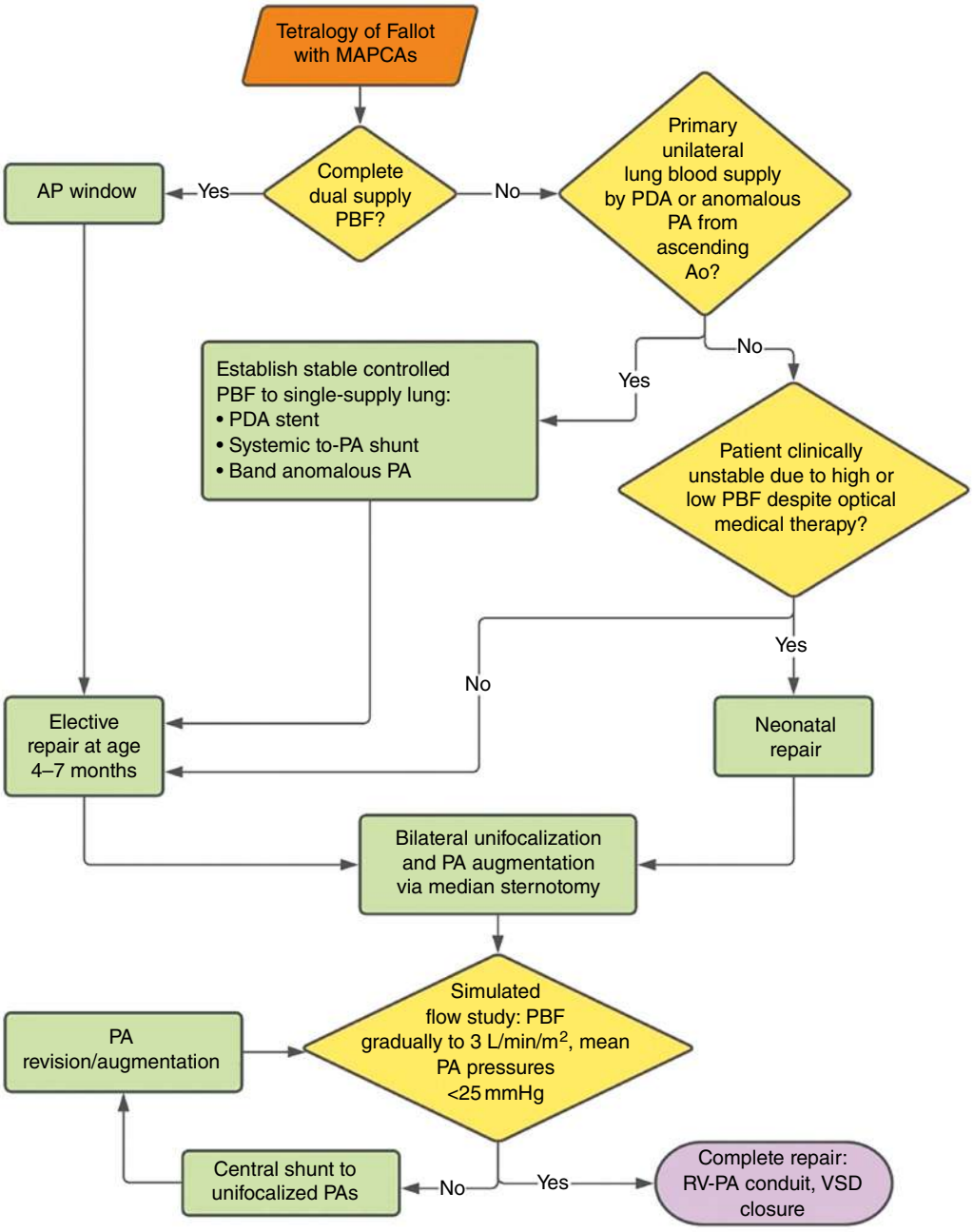


Figure 28.25 Algorithm for management of newborns with tetralogy of Fallot and major aortopulmonary collateral arteries from Lucille Packard Children's Hospital [123]. Ao, aorta; AP, aortopulmonary; MAPCAs, major aortopulmonary collateral arteries; PA, pulmonary artery; PDA, patent ductus arteriosus; PBF, pulmonary blood flow; RV, right ventricle; VSD, ventricular septal defect. (Source: Michael L. Schmitz, MD.)

- Significant pulmonary overcirculation resulting in severe failure to thrive: Unifocalization is usually done in this situation.
- Profound hypoxia (usually due to proximal MAPCA stenoses with or without native BPAs): If patients have significant native BPA tissue, yet proximal stenoses in MAPCAs, surgical palliation may be accomplished via unifocalization. On the other hand, patients with limited native BPA tissue are poor surgical candidates for early complete palliation and future prognosis to obtain biventricular physiology is poor [129].

"Unifocalization" refers to the process of dividing MAPCAs from their aortic origin and anastomosing them directly to the native BPAs or to a homograft or tube graft conduit connecting to the pulmonary arteries [124] (Figure 28.26). As mentioned, unifocalization is usually performed in infancy but occasionally in the neonatal period. Midline sternotomy is the common approach, although thoracotomy (usually on the side of the descending aorta) may be necessary to initially access MAPCAs lying posteriorly or within lung fissures. Previously, multistage procedures were often performed with sequential bilateral thoracotomies

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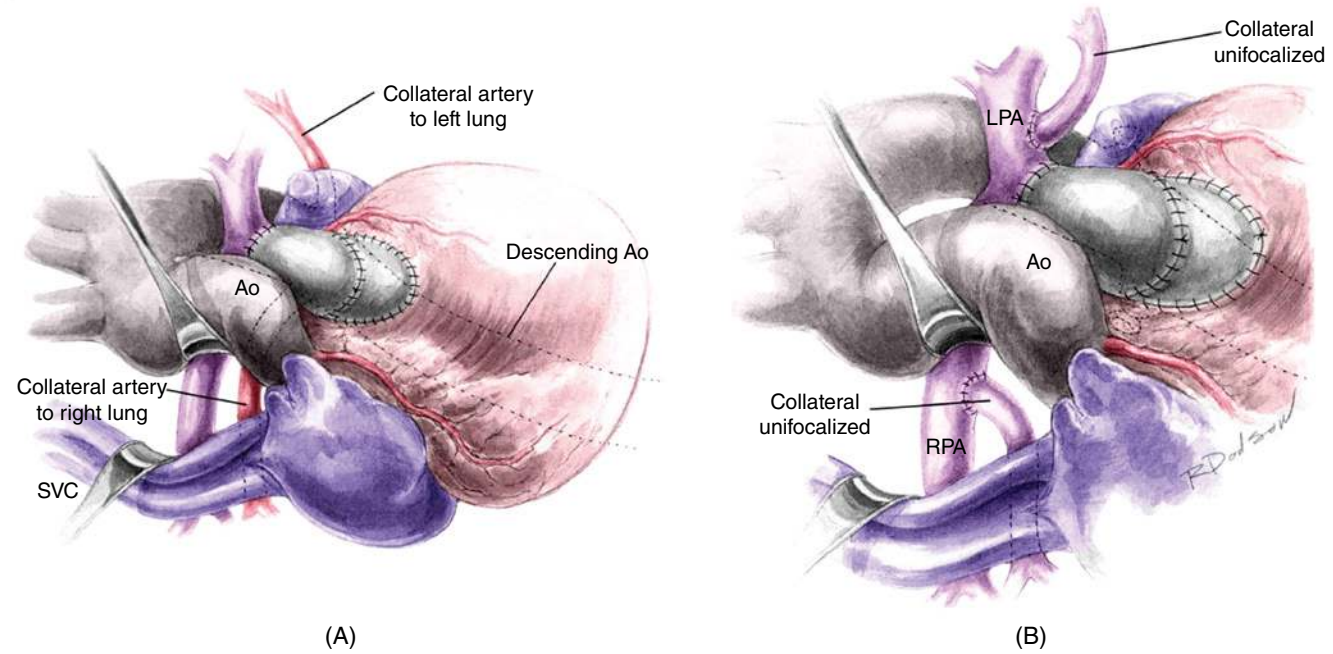


Figure 28.26 Unifocalization of collateral arteries to true pulmonary arteries via a median sternotomy. (A) As the aorta (A0) is retracted to the left, a collateral artery to the right lung is seen posterior to the transverse sinus. (B) One collateral artery has been unifocalized to the true right pulmonary artery (RPA) and another collateral artery has been unifocalized to the left pulmonary artery (LPA). SVC, superior vena cava. (Source: Jonas [124]. Reproduced with permission of Taylor & Francis.)

followed by a midline sternotomy approach that might include intracardiac repair. Single-stage unifocalization with or without an intial thoracotomy, sometimes including intracardiac repair, has shown excellent results [130]. In a review of patients who underwent single-stage midline unifocalization, Mainwaring et al. identified predictors for later need for unifocalization revision. These predictors included increased PBF augmentation with a systemic-to-pulmonary artery shunt, a higher RV:aorta pressure ratio (0.44 ± 0.08 versus 0.33 ± 0.07), or absence of central pulmonary arteries (32.8% versus 13.4%) [129]. Regardless of approach, it is essential to isolate and control all significant MAPCAs with vessel loops prior to going on CPB as systemic and cerebral hypoperfusion can occur despite adequate CPB flow as blood volume is lost into the pulmonary vasculature via open MAPCAs. A single-stage approach is not feasible in all patients (see neonatal repairs above); some require a systemic-to-pulmonary artery shunt or an RV-to-pulmonary artery conduit to allow growth before definitive repair.

Several single-center outcome analyses of surgical repair of TOF/PA have been published in the last decade. While some advocate using MAPCAs for reconstructing the pulmonary blood supply (MAPCA-based PBF), others are against using MAPCAs due to concerns of long-term reliability for PBF as they are prone to proximal stenosis. Therefore, two main management strategies have evolved: (i) to recruit all sources of PBF and focus on early intervention and midline single-stage unifocalization [123] and (ii) to focus on native pulmonary arterial rehabilitation and not utilize MAPCAs. In the second strategy, a central connection via aortopulmonary shunt or RV-pulmonary artery conduit is used to provide antegrade perfusion and hopeful future pulmonary vascular bed growth [130]. Serial balloon dilations and possible stenting are performed in the hopes of achieving appropriate RV/LV pressure ratio and subsequent intracardiac repair.

Of note, some centers have noted good early and late results regarding RV/LV pressure ratio utilizing MAPCA-based PBF [127]. While historical analysis of MAPCA-based circulations has shown poor late outcomes, it has been hypothesized that early intervention in the neonatal period and infancy (versus intervention at older ages) may lead to decreased arterial shear force and potential overcirculation, and thus improved late clinical outcomes [123].

Anesthetic considerations

Preoperative

The anesthetic management is based on the surgical procedure, including a range from shunts and PDA stents to unifocalization via thoracotomy or midline sternotomy. Principles for induction, maintenance and monitoring are similar to those described above for repair/palliation of TOF, however there are unique considerations. Anesthetic management for central systemic-to-pulmonary artery shunts placement, PDA stenting, and RV-to-pulmonary artery conduit placement are discussed earlier. Anesthetic management for single-stage palliation with unifocalization via median sternotomy follows.

Patients with TOF/PA/MAPCAs have variable complexity owing to severity of disease. Preoperative oxygenation, Qp:Qs, and cardiac function can be obtained from cardiac catheterization data [131]. Qp/Qs is largely influenced by MAPCA size and their associated PBF. Large, unobstructed

MAPCAs can result in overcirculation to the point of CHF. On the other hand, tortuous MAPCAs and those with proximal stenoses can result in cyanosis and metabolic acidosis.

Chromosome 22q11 deletion is commonly present and may be associated with hypocalcemia as well as a difficult airway due to a small mouth opening, micrognathia, subglottic stenosis, glottic web, laryngeal paralysis, larygomalacia associated with bronchial malposition, and velopharyngeal and palate defects [131–133]. Basic laboratory data, including complete blood count with differential, basic metabolic panel; coagulation studies; ECG, chest radiograph, imaging as transthoracic echocardiography; CT and MRI results; cardiac catheterization data; and prior anesthetic records are reviewed prior to surgery [134].

Intraoperative

Most patients tolerate a slow, controlled inhalational induction with sevoflurane [90], with FiO_2 adjusted to maintain an oxygen saturation of 75–85% to balance Qp:Qs. Standard monitors are utilized. Those with airway abnormalities should be anticipated, requiring advanced airway devices such as video laryngoscopy. As MAPCA development can be associated with tortuous peripheral vessel development, percutaneous vascular access can be difficult [134] but facilitated with bedside ultrasound guidance for both arterial and venous access.

Administration of anesthetic drugs during repair requires careful consideration. Considerable pulmonary runoff can occur from large MAPCAs; therefore, maintaining adequate systemic perfusion pressure is important to prevent systemic acidosis and hypoxemia from hypoperfused collateral arteries. A total or near-total IV technique with various agents (narcotics, benzodiazepines, dexmedetomidine, neuromuscular blocker) may be preferred to avoid decreases in mean arterial blood pressure (MABP), SVR, and CO that can occur with inhaled anesthetic agents in a dose-dependent fashion. Use of high dose narcotic anesthetic regimens (>50 μg/kg) as the primary anesthetic in congenital cardiac surgery can provide hemodynamic stability.

Dissection and ligation of collaterals is usually done off CPB to minimize total CPB time, provided the patient does not experience extreme hypoxia and metabolic acidosis [134]. This portion of the procedure may be prolonged (4–6 hours). With each MAPCA ligation, PBF is subtracted and redistributed to the systemic circulation, creating desaturation and hemodynamic changes. Careful monitoring of respiratory and hemodynamic parameters is required as large changes in oxygenation, ventilation, systemic perfusion, and cardiac arrhythmias may occur. A TEE probe may be placed, but if the patient is at risk for tracheobronchial compression, TEE should be omitted. Correction of metabolic and respiratory acidosis, maintenance of adequate circulating hemoglobin, and use of low-dose inotropic drugs may be useful during off-CPB dissection to maintain adequate oxygenation and perfusion.

Anesthetic management on CPB is similar to that of TOF (see previous section) with the caveat that residual open MAPCAs can cause hemodynamic instability on CPB due to shunting of arterial blood away from vital organs and loss of blood volume into the pulmonary vasculature. The target MABP is higher than usual for neonatal/infant repairs (60–70 mmHg) to ensure end-organ perfusion. Evidence of adequate end-organ perfusion is estimated by NIRS trends, urine output and ABG analysis. Some centers conduct an intraoperative PBF study to ensure appropriate RV/LV pressure ratios prior to intracardiac repair [135].

After cessation of CPB, reperfusion injury may occur in the lung segments that experienced low perfusion preoperatively which can impact hemostasis and worsen pulmonary compliance due to increased dead space ventilation from tracheobronchioalveolar pulmonary edema and intraparenchymal bleeding [134]. Frequent suction, aggressive pulmonary toilet and maintenance of appropriate PEEP may be useful to improve oxygenation and ventilation. Inotropic drugs as milrinone and epinephrine are commonly used to decrease PVR/improve lusitropy, and enhance CO respectively in a potentially stressed RV. To further reduce PVR, iNO may be necessary to improve oxygenation and CO. Blood loss can be significant secondary to extensive dissection, CPB time, and multiple suture lines. Ready transfusion with blood products to restore coagulation and replace hemoglobin losses is imperative.

Postoperative

Postoperatively, patients remain on mechanical ventilation with inotropic support. Aggressive pain control with opioid infusions and/or regional anesthesia and sedation with benzodiazepine and dexmedetomidine infusions are useful to minimize systemic and pulmonary hypertension. Continued aggressive management of postoperative bleeding is often necessary with prompt transfusion and correction of developing coagulopathies.

KEY POINTS: PULMONARY ATRESIA/ VENTRICULAR SEPTAL DEFECT/MAJOR AORTOPULMONARY COLLATERAL ARTERIES

- Biventricular repair consists of constructing a pulmonary bed using various available sources of PBF, connecting the RV to the new pulmonary bed, and closing the VSD.
- The successful post-biventricular repair requires an RV systolic pressure ≤50% of LV systolic pressure.
- Prepare for major blood loss and replacement.
- Ventilation can be compromised from intrapulmonary and airway bleeding from multiple anastomoses and/or lung reperfusion injury.
- RV dysfunction from increased afterload is treated with adequate preload, inotropic support, and ventilation adjustments/iNO to reduce PVR.

Summary

Right-sided obstructive congenital cardiac lesions comprise a range of heart defects associated with variable clinical manifestations. The pattern and severity of the structural anomalies determine the presentation of the patient on the symptomatology spectrum, from a neonate with cyanosis, CHF and ductal-dependent circulation, to the young adult

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with mild to moderate exercise intolerance. The presence of a septal defect is nearly universal in this group of lesions and confers the potential for right-to-left intracardiac shunt. One lesion, TOF–the archetype of CHD, leads the way for the evolution of multifaceted diagnostic and therapeutic advances while charting the unknown territory of long-term outcomes beyond survival. The optimal perioperative anesthetic management for the patient with a right-sided obstructive congenital heart lesion requires an understanding of the anatomy and pathophysiology of the cardiac lesion, the implications of the proposed surgical maneuvers, and the effects of the anesthetic and ventilatory techniques in dynamic interaction with other factors. Most patients with CHD have limited cardiopulmonary reserve; thereby, anticipation of complications with preparation for prevention and rescue are critical for improved outcomes.

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Markus S. Renno, M.D. – Figure 28.24

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

10 Hoffman JE (ed.) *The Natural and Unnatural History of Congenital Heart Disease*. West Sussex, UK: Wiley-Blackwell, 2009. A rather unique textbook, Dr. Hoffman took on the enormous task of describing congenital heart disease in terms of what happens in the course of congenital heart disease with and without treatment. And, for those who underwent treatment, descriptions of the disease course are described based on the available treatments that were chosen.

23 Holst KA, Connolly HM, Dearani JA. Ebstein's anomaly. Methodist DeBakey Cardiovasc J 2019;15:138–44. This is a thorough review of the preoperative evaluation including the kinds of details found on echocardiogram, computed tomography, and magnetic resonance imaging that impact the surgical plan. The surgical description of the cone procedure is the current state-of-the-art with excellent details.

75 Sandoval N, Carreño M, Novick WM, et al. Tetralogy of Fallot repair in developing countries: international quality improvement collaborative. Ann Thorac Surg. 2018;106:1446–51. This report analyzed 2,164 patients undergoing TOF repair from a database of 32 centers in 20 low-to-middle income countries. Important metrics were identified for benchmarking and improving surgical outcomes in resource-limited nations.

80 Morales DL, Zafar F, Fraser CD. Tetralogy of Fallot repair: the right ventricle infundibulum sparing (RVIS) strategy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2009;12:54–8. The authors present a comprehensive strategy to repair TOF with the goals of preserving RVOT integrity to decrease the long-term morbidity associated with the traditional approach of large ventriculotomy and transannular resection.

96 Ghimire L, Chou F. Efficacy of prophylactic dexmedetomidine in preventing postoperative junctional ectopic tachycardia in pediatric cardiac surgery patients: a systematic review and meta-analysis. Pediatr Anesth 2018;28:597–606. This meta-analysis found that prophylactic dexmedetomidine use was effective in decreasing the rate of junctional ectopic tachycardia following pediatric cardiac surgery without significant increases in adverse events.

104 Winch P, Staudt A, Sebastian R, et al. Learning from experience: improving early tracheal extubation success after congenital cardiac surgery. Pediatr Crit Care Med 2016;17:630–7. The authors analyzed early tracheal extubation failures after congenital cardiac surgery and found that re-intubation was associated with increased morbidity, hospital stay and mortality. They observed that re-intubation may be related to postoperative delirium and conclude that implementation of robust protocols to address delirium and pain are key to successful outcomes.

108 Cuypers JAAE, Witsenburg M, van der Linde D, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. Heart 2013;99:339–47. A thorough review of clinical recommendations for diagnosis and treatment of patients with pulmonary stenosis.

118 Gleich S, Latham GJ, Joffe D, Ross FJ. Perioperative and anesthetic considerations in pulmonary atresia with intact ventricular septum. Semin Cardiothorac Vasc Anesth 2018;22:256–64. This article is a well written overview of perioperative and anesthetic management of patients with PA/IVS.

123 Ma M, Mainwaring RD, Hanley FL. Comprehensive management of major aortopulmonary collaterals in the repair of tetralogy of Fallot. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2018;21:75–82. This is an in-depth review of evolution of surgical technique, comparison of management strategies, and discussion of long-term outcomes and current clinical controversies for patients with TOF/MAPCAs.

134 Quinonez ZA, Downey L, Abbasi RK, et al. Anesthetic management during surgery for tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries. World J Pediatr Congenit Heart Surg 2018;9:236–41. This article presents a clear synopsis of the complex anesthetic management of patients with TOF/PA/MAPCAs at a quaternary care referral center.

CHAPTER 29

Anesthesia for Transposition of the Great Arteries

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Introduction

Transposition of the great arteries (TGA) refers to a spectrum of conditions of discordant ventriculoarterial (VA) connections. The term TGA is most commonly used to denote concordant atrioventricular (AV) connection and discordant VA connection, where the aorta arises from the morphological right ventricle and the pulmonary artery from the morphological left ventricle. This is the most common anatomic form encountered in clinical practice and is referred to as dextro-TGA, or d-TGA. The term TGA also encompasses the hearts with discordant AV and VA connections known as congenitally corrected TGA (or ccTGA, levo- or l-TGA) and more rarely, other forms of anomalous AV connections.

TGA is the second most common congenital cardiac lesion, which accounts for approximately 6% of all congenital heart defects [1]. It is frequently an isolated lesion with no other associated extracardiac anomalies. Medical and surgical advances in the past four decades have spectacularly improved the outcome for individuals born with these lesions, from what was a universally lethal condition, into one of expected survival with the ability to lead near-normal lives.

Initial attempts at anatomical repair were associated with poor outcome, leading to the development of physiological repair by Mustard and Senning. Today, the arterial switch operation (ASO) is the mainstay of management of these patients, with excellent results. Surgical intervention requires the cardiac anesthesiologist to fully understand the pathophysiology, aims of treatment, surgical procedures, and postoperative consequences to form the perioperative management plan.

This chapter will address two main subcategories of transposition: physiologically uncorrected TGA (referred to as TGA or d-TGA) and congenitally corrected TGA (ccTGA or l-TGA).

KEY POINTS: INTRODUCTION

- TGA refers to a spectrum of conditions of discordant VA connections.
- The two main categories are physiologically uncorrected (d-TGA) and congenitally corrected (ccTGA or l-TGA).
- The outcome of d-TGA is very good, with patients expecting to lead near-normal lives.

Physiologically uncorrected TGA

Incidence

TGA accounts for 5–7% of all congenital heart defects with a prevalence of 0.2 per 1,000 live births [1, 2]. There is a male preponderance of 2–3:1, and sibling recurrence rates of between 0.27 and 1.8% have been noted [3].

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Anatomy

Physiologically uncorrected transposition of the great arteries is the most common anatomic form encountered in clinical practice and is referred to as TGA or d-TGA. In other words, the normal connections of right atrium (RA) to right ventricle (RV) and left atrium (LA) to left ventricle (LV) are preserved, but there is VA discordance: the aorta arises from the RV rather than LV and the pulmonary artery (PA) from the LV (Figure 29.1).

This definition encompasses a spectrum of cardiac anomalies that can be further subdivided into either simple or complex TGA (Figure 29.2). In approximately 50–75% of cases children present with simple TGA in which there is isolated VA (VA) discordance with either a patent foramen ovale (PFO) or patent ductus arteriosus (PDA) or both. This is referred to as TGA with intact ventricular septum (TGA/IVS).

The lesion is considered a complex TGA when it has associated cardiac abnormalities. Complex TGA occurs in 25% of the patients with D-TGA and requires alternative management and operative planning. Cardiac anomalies included in complex TGA are as follows:

- Ventricular septal defect (VSD), 40%
- Left ventricular outflow tract obstruction (LVOTO), 5%
- Double outlet right ventricle and the Taussig–Bing malformation
- Rarer abnormalities, which include TGA with VSD and coarctation of the aorta 5% or TGA with VSD and interrupted aortic arch.

The focus of this chapter will be on the most common and important clinical subsets:

- TGA with intact ventricular septum (TGA/IVS)
- TGA with VSD including the Taussig–Bing malformation
- TGA with LVOTO
- TGA and pulmonary vascular obstructive disease

In the normal heart, the position of the aorta is posterior and to the right of the pulmonary trunk. There is a

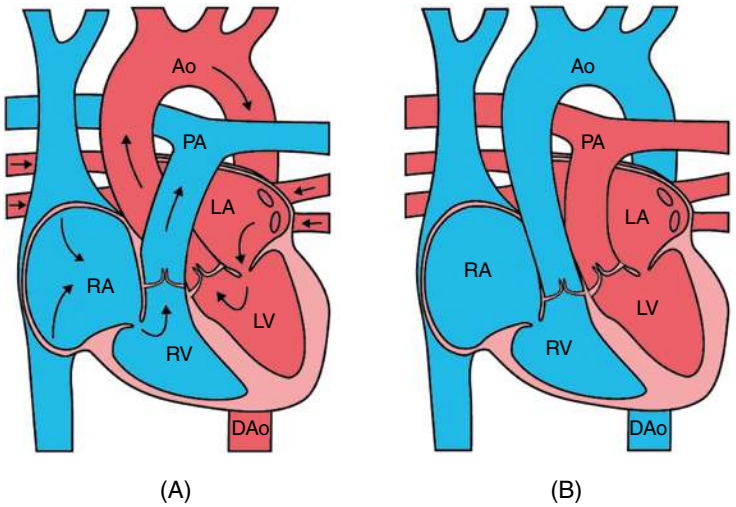


Figure 29.1 Dextro-transposition of the great arteries (d-TGA). (A) Normal anatomy. (B) d-TGA anatomy. Ao, aorta; PA, pulmonary artery; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; DAo, descending aorta.

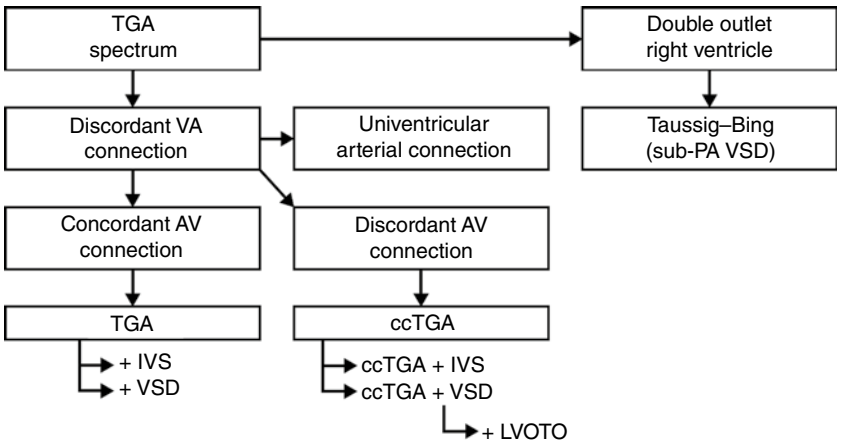


Figure 29.2 The spectrum of discordant ventriculoarterial connections that come under the "umbrella" of the term transposition of the great arteries (TGA). AV, atrioventricular; VA, ventriculoarterial; PA, pulmonary artery; VSD, ventricular septal defect; IVS, intact ventricular septum; ccTGA, congenitally corrected transposition of the great arteries; LVOTO, left ventricular outflow tract obstruction.

subpulmonary muscular infundibulum, and the annulus of the aortic valve is in fibrous continuity with the mitral valve annulus. In the most common manifestation of TGA, a right sided right atrium connects via a right sided tricuspid valve and RV to a right sided and anterior aorta. There is a subaortic muscular infundibulum. On the left, a left-sided atrium connects via the mitral valve and LV to a left-sided and posterior PA. As a result, there is fibrous continuity between the mitral and pulmonary valves, but no fibrous continuity between the tricuspid and aortic valves [4, 5]. This anatomical manifestation is commonly referred to as d- or dextro-TGA with the position of the aorta being anterior and to the right of the pulmonary trunk. However, in strict anatomical terms, d- or dextro-TGA describes patients who have [S,D,D] segmental anatomy, meaning situs solitus [S], d-loop ventricles [D], and d-loop great arteries [D].

Although VSDs are detected in up to 30–40% of patients with TGA using angiography, only about one-third of these are hemodynamically significant [6]. Approximately one-third of the VSDs are perimembranous, and another one-third are outlet VSDs with malalignment. From a surgical perspective, outlet VSDs with malalignment are more difficult to repair. In the presence of a VSD, the aorta is generally smaller than the PA; this discrepancy in size tends to be amplified in the presence of an anterior maligned VSD. Conversely, LVOTO is common when there is posterior deviation of the outlet septum.

The Taussig–Bing anomaly (TBA) represents a complex subset of double outlet right ventricle (DORV) with subpulmonary VSD that behaves as a physiological TGA. It is not theoretically a TGA, as the VA connection is double outlet, however, it is so similar to TGA from a physiological and management perspective that it is included within the TGA subset. In TBA, there is DORV with subpulmonary VSD, side-by-side vessels, and bilateral conus [7]. The aorta originates from the RV, and the PA arises from above the nonrestrictive VSD. It is frequently associated with subaortic right ventricular outflow tract obstruction (RVOTO) because of hypertrophy of the infundibular septum and aortic arch obstruction. Left ventricular oxygenated blood is preferentially streamed into the PA, thereby simulating TGA physiology.

Anatomic LVOTO can be found in approximately one-third of patients with TGA and VSD, but it is rare in TGA/IVS, with an incidence of approximately 0.7%. Anatomic LVOTO can arise at the valvular or subvalvular level and can be caused by several anatomical structures. Valvular obstruction might be secondary to commissural fusion, annular hypoplasia, or leaflet immobility from a hypertrophic tissue [6, 8]. Pulmonary subvalvular obstruction may be attributable to posterior displacement of the conal septum, a subvalvular fibrous membrane, accessory leaflet tissue of the AV valve, or diffuse hypoplasia of the left ventricular outflow tract (LVOT). In TGA/IVS, mechanical LVOTO is uncommon, but 5% patients have functional LVOTO. This occurs due to the presence of a high systemic right ventricular pressure, displacing the interventricular septum into the LV during systole. This is uncommon in neonates as the septal shift required is prevented by their high pulmonary vascular resistance [9]. LVOTO limits pulmonary blood flow and therefore exacerbates the cyanosis in TGA.

Coronary artery anatomy

Coronary artery anatomy is extremely important in d-TGA patients as transfer of the coronary arteries to the neo-aorta without narrowing or distortion is critical to the success of an arterial switch operation (ASO). Mortality from distortion of the newly implanted coronary arteries arises from myocardial ischemia; necrosis of the supplied myocardial segment may cause fatal arrythmias, such as ventricular fibrillation [10]. The critical importance of unrestricted aortocoronary blood flow after ASO was established during the earliest unsuccessful ASOs in the 1950s by William T. Mustard [11, 12]. Initially the ASO was associated with 100% mortality. In 1954, three patients underwent ASO, a 6-week-old child died from aortic suture line bleeding, a 19-day-old died from left coronary artery occlusion, and another 19-day-old died from ventricular fibrillation [13].

In the normal heart, the coronary arteries arise from the aortic sinuses of Valsalva, which face the PA and are located on the anterior portion of the aorta (Figure 29.3). In TGA, the coronary arteries also arise from the aortic sinuses of Valsalva, but the location of the sinuses is posterior [4]. Considerable variability exists in the origin, distribution, and epicardial course of coronary artery anatomy in d-TGA. The Leiden classification (Figure 29.4) system appears most commonly in surgical literature and is used to demonstrate the frequent coronary patterns that exist in TGA [16].

Although all types of coronary anatomy are suitable for the ASO, the less common coronary patterns present potential technical difficulties for an ASO and a moderately increased risk [17]. Single right coronary artery, inverted coronary artery, and coronary arteries with an intramural course have been identified as carrying increased risk [17, 18], but recent studies have shown that with increased surgical experience, coronary artery pattern may not be a risk factor for increased morbidity following the ASO [19, 20].

KEY POINTS: ANATOMY OF D-TGA

- In d-TGA, there is concordant AV connection and discordant VA connection.
- The aorta arises from the morphological RV and the PA from the morphological LV.
- Approximately 75% have simple TGA: isolated VA discordance with a PFO, PDA, or both.
- Complex TGA has VSD, LVOTO, or Taussig–Bing malformation.
- Coronary anatomy has considerable variability in its origins and distribution.

Natural history and pathophysiology

In the normal circulation, blood circulates in series; deoxygenated blood from the systemic circulation enters the right heart and proceeds to the lungs via the PA. Oxygenated blood then returns from the lungs via the pulmonary veins to the LA and is pumped through the LV to the systemic circulation via the aorta. In TGA, there is AV concordance (RA→RV and LA→LV) but VA discordance (LV→PA and RV → aorta) resulting in two parallel circulations (Figure 29.5). Blood flows in a

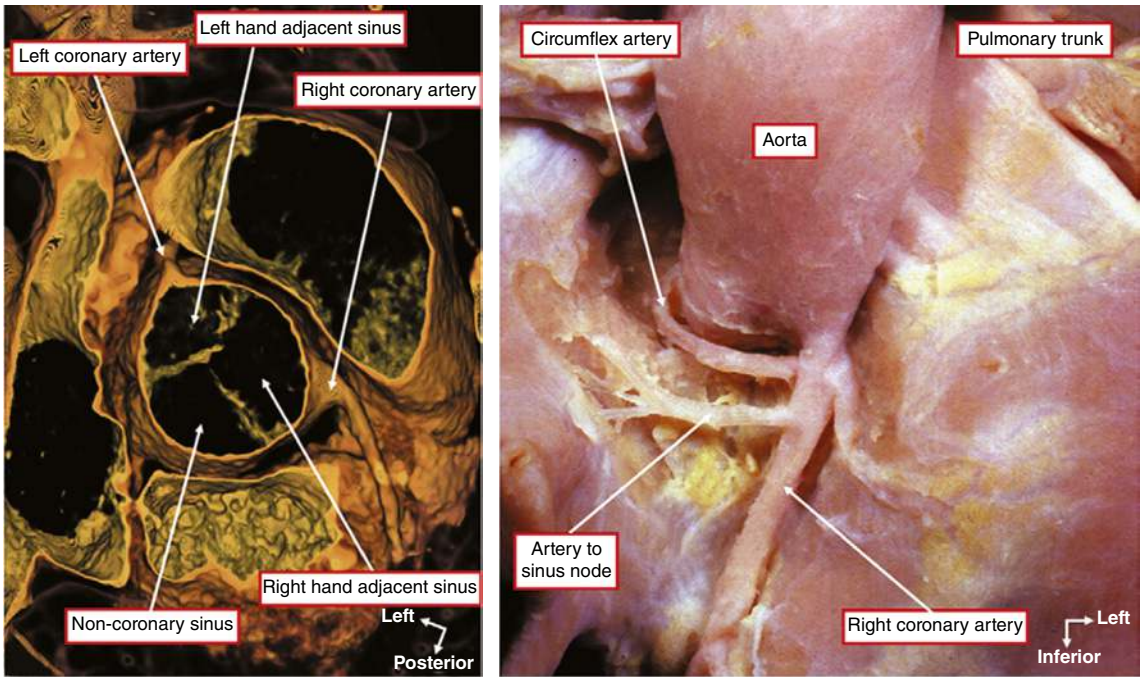


Figure 29.3 Anatomy of normal coronary arteries is well shown by computed tomography. (A) The aortic root as viewed from above. Right and left coronary arteries arise from the aortic valvular sinuses adjacent to the subpulmonary infundibulum, which has been transected to provide this image. (B) Variant in an otherwise normal heart in which the circumflex coronary artery arises from the right coronary artery and then extends through the transverse sinus. (Source: Chiu & Anderson [14]. Reproduced with permission of Elsevier.)

closed circuit on both sides of the heart where deoxygenated blood is recirculated to the body without passing the lungs for oxygenation. Oxygenated blood from the left side of the heart returns back to the lungs via the PA without reaching the body. Without one or more communications that allow for intercirculatory mixing, survival would be impossible. If left untreated, death from hypoxia and congestive heart failure (CHF) will occur in 90% of patients within the first year of life.

Shunting and effective pulmonary and systemic blood flow in TGA

In TGA, the parallel circulations mean that, without shunting, no oxygenated blood would reach the tissues or deoxygenated blood the lungs. Anatomical shunting occurs due to a communication at the level of the cardiac chambers or great vessels allowing blood to move from one circulation to the other. A physiological shunt occurs when blood is recirculated and is considered "surplus" and noneffective. For example, a physiological left to right shunt is all the blood that is recirculated through the pulmonary vascular bed (the LA to the PA avoiding the systemic circulation). Physiological right-to-left shunt occurs through the recirculation of systemic venous blood (RA to the aorta, avoiding the pulmonary circulation). Therefore, in TGA, the majority of the blood flow is physiological shunt (recirculated blood that is ineffective) with a small proportion of blood that travels across the anatomical shunt (in effect, making up the effective blood flow) (Figure 29.6) [21]. The effective blood flow is the flow necessary for survival and comprises blood from the venous system of one circulation that reaches the arterial system of the other.

- **Effective pulmonary blood flow** is the amount of systemic venous blood that reaches the pulmonary arterial bed (e.g., *in TGA, an anatomic R-to-L shunt)*
- **Effective systemic blood flow** is the amount of pulmonary venous blood that reaches the arterial systemic circulation (e.g., *in TGA, an anatomic L-to-R shunt)*

Note: When bidirectional shunting occurs, the anatomic and effective blood flows are not equal. This is because some of the anatomic shunted blood may be redirected back to its original venous side prior to reach the arterial side of the other circulation. [21]

Effective pulmonary blood flow and effective systemic blood flow must be equal or one of the circulations would become deplete. Total pulmonary circulation is the volume of recirculated pulmonary venous blood and effective pulmonary blood flow. Total systemic blood flow is the volume of recirculated systemic blood and effective systemic blood flow. The greater the volume of the effective systemic blood flow relative to the recirculated flow, the greater is the arterial oxygen saturation. In contrast to effective blood flow, total pulmonary blood and total systemic blood flow do not have to be equal. This is most evident in the pulmonary circulation, where the total pulmonary blood flow is 2 to 3 times that of the total systemic blood flow (Qp:Qs 2–3:1). When there is adequate mixing of pulmonary and systemic venous blood, the arterial oxygen saturation is influenced by the Qp:Qs ratio. A high Qp will result in a pulmonary artery saturation that is higher than the aortic oxygen saturation, and systemic hypoxia will not occur. If there is effective mixing but pulmonary blood flow is restricted (due to LVOTO or PAH), the Qp:Qs ratio will drop below 2, significantly lowering the systemic arterial saturation

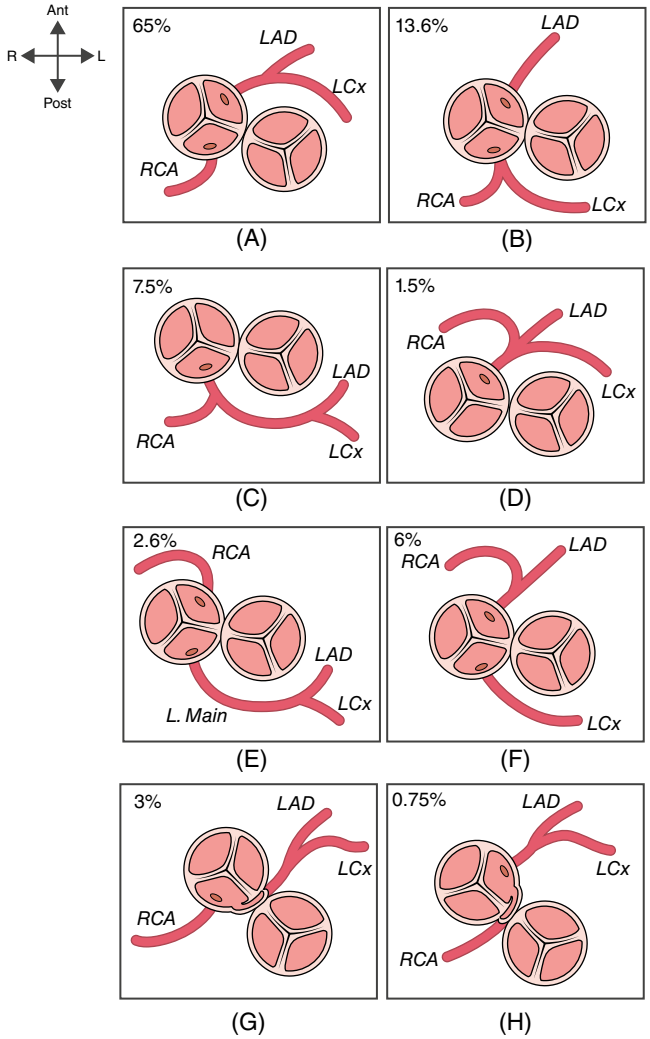


Figure 29.4 The most common patterns of coronary anatomy in patients with D-loop transposition of the great arteries (TGA). (A) Usual coronary anatomy with the left coronary artery (LCA) arising from sinus 1 and the right coronary artery (RCA) from sinus 2. (B) Left circumflex coronary artery (LCx) arising from the RCA (sinus 2) and the left anterior descending (LAD) from sinus 1. (C) Single coronary from sinus 2. (D) Single coronary artery arising from sinus 1. (E) Inverted origin with the RCA arising from sinus 1 and the LCA from sinus 2. (F) The LAD and RCA arising from sinus 1 and the LCx from sinus 2. (G) Intramural LCA with origin of the LCA and RCA both from sinus 2 and intramural course of the LCA. (H) Intramural RCA with origin of the RCA and LCA from sinus 1 and intramural course of the RCA. (Source: Mertens et al. [15]. Reproduced with permission of John Wiley & Sons.)

and causing severe hypoxia [22]. These concepts are vital in understanding the physiology in TGA circulation.

Intercirculatory mixing

Intercirculatory mixing can occur at one or more intracardiac (PFO/ASD or VSD) or extra-cardiac (PDA or bronchopulmonary collaterals) sites. The degree of intercirculatory mixing is one of the factors that influences hemoglobin oxygen saturation and hence tissue oxygen delivery. In the first few days of life, the degree of cyanosis and the stability of the child will be largely determined based on the degree of mixing that occurs between the two parallel circulations, which in turn will determine the neonate's course, medical management, and surgical timing.

Intercirculatory mixing is dependent on multiple factors in the neonatal period, namely the number, size, and position of the anatomic communications (Table 29.1). Larger, unrestrictive, and multiple communications allow for improved intercirculatory mixing. Although there is significant interplay between these factors, one large communication will allow for better mixing than two or more restrictive ones and a large but unfavorably positioned VSD, namely an anterior muscular VSD, is not conducive to effective mixing. [23]

Physiological factors have a significant impact on mixing, including ventricular compliance, systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). Balancing the effective pulmonary and systemic blood flows allows for optimal intercirculatory mixing. At the level of the atria, shunting is mainly influenced by the size of the ASD and the pressure variations across it. Mixing here is the most efficient as lower pressures allow for bidirectional flow during the cardiac cycle; for this physiologic reason, balloon atrial septostomy (BAS – see below) is preferred for cyanotic d-TGA patients. Conversely, mixing at a VSD or PDA is usually more restricted as larger pressure gradients exist, typically directing blood in one direction (usually from right to left).

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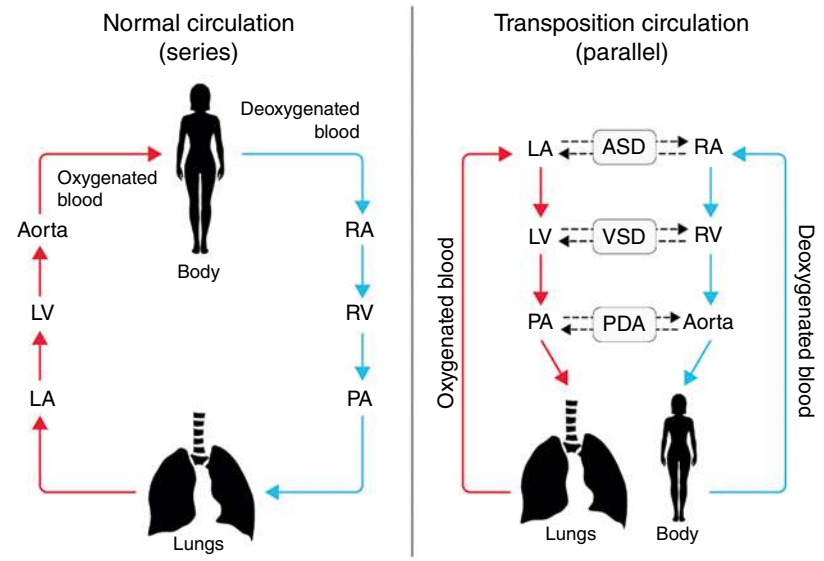


Figure 29.5 Comparison of the normal circulation, which is in series, with that in transposition of the great arteries (TGA), which is in parallel. In the normal circulation (left), deoxygenated blood from the body enters the right-sided circulation before being oxygenated by the lungs and then distributed to the body via the left side of the heart. In the transposition circulation (right), the potential sites of mixing are shown: atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). The circulation is in parallel; thus, deoxygenated blood from the body enters the right side of the heart, but because of the anomalous connection, it is recirculated to the body via the aorta. Similarly, the oxygenated blood from the lungs enters the left heart but is recirculated to the lungs via the PA. This condition would be incompatible with life, if there was not any mixing of the oxygenated and deoxygenated blood. RA, right atrium; RV, right ventricle; PA, pulmonary artery.

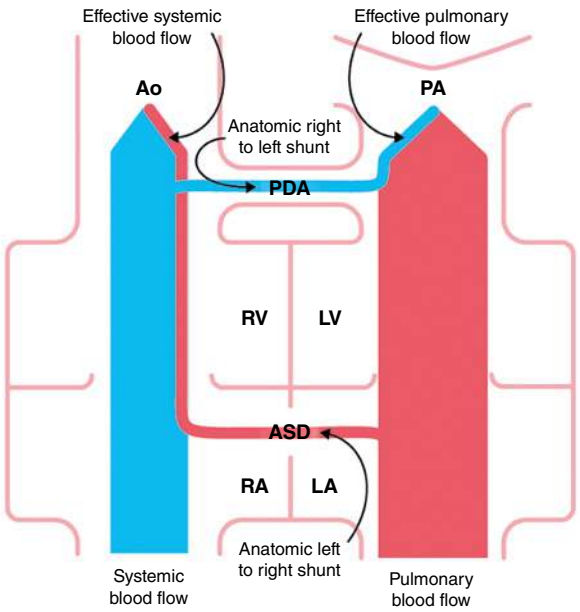


Figure 29.6 Representation of intracardiac shunting in transposition of the great arteries with intact ventricular septum (TGA/IVS), unrestrictive atrial septum, and PDA. The majority of flow is recirculated, RA→aorta and LA →PA, and is therefore, ineffective. A small amount of blood shunts left-to-right via the ASD; this is effective systemic blood flow. Equally, a small amount of blood flows from the aorta to the PA via the PDA, this is effective pulmonary blood flow. The effective systemic and pulmonary blood flows are equal and constitute a small volume of flow that is necessary for life. Typically, the total pulmonary blood flow is 2 to 3 times greater than the total systemic blood flow. AO, aorta; PA, pulmonary artery; ASD, atrial septal defect; LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle; PDA, patent ductus arteriosus.

Table 29.1 Factors influencing intercirculatory mixing in patients with D-TGA

Factor	Effect on mixing
Size	• Mixing improved by larger, unrestrictive communications
Position	• More efficient mixing at the atria due to lower pressure • Poor mixing at anterior muscular VSDs due to unfavorable position
Number	• Greater number of communications increases intercirculatory mixing
Pulmonary blood flow	• High pulmonary flow is associated with maximal mixing

Pulmonary blood flow

The efficiency of mixing is further influenced by total pulmonary blood flow (Qp) [23]. As the patient surpasses the neonatal period, pulmonary blood flow is increasingly important in determining intercirculatory mixing. As PVR continues to drop after the neonatal period, cyanosis tends to improve. This may occur as the decrease in PVR increases pulmonary blood flow, thus increasing mixing. The opposite may also to be true: as pulmonary blood flow is reduced (usually secondary to pulmonary stenosis or pulmonary vascular occlusive disease), a decrease in mixing occurs resulting in a drop in systemic arterial saturation [23, 24]. A reduction in pulmonary blood flow caused by a decrease in overall cardiac output (e.g., hypovolemia, depressed myocardial contractility from volatile anesthetics) will also exacerbate cyanosis.

TGA and pulmonary vascular occlusive disease

Children with TGA are at particular risk of developing pulmonary vascular occlusive disease compared with other congenital heart lesions, especially in TGA with VSD. Pulmonary vascular remodeling caused by an abnormal hemodynamic state [25] (i.e., high pulmonary blood flow) plays a significant role in the development of pulmonary vascular occlusive disease. Multiple other factors believed to contribute to this disease process also exist in these patients: hypoxemia, polycythemia, and high PA pressure [6].

As PVR increases and pulmonary hypertension develops, pulmonary blood flow is reduced, thereby decreasing intercirculatory mixing and worsening systemic hypoxemia. Late diagnosis of TGA may result in severe pulmonary vascular occlusive disease. Once pulmonary hypertension is established, the therapeutic surgical options are reduced, sometimes necessitating palliative rather than curative options.

Flow characteristics and intercirculatory mixing vary depending on the variations in anatomy of the TGA subsets.

TGA with intact ventricular septum

In TGA/IVS, intercirculatory mixing occurs at two main sites: ASD and PDA. In TGA/IVS without additional communications (i.e., no PDA), shunting at the atrium is predominantly dependent on the size and pressure gradients across the atrial communication. During systole blood shunts from the LA to the RA (effective systemic blood flow) due to a raised LAP from the high volume of recirculating pulmonary blood flow. During diastole blood shunts from the RA to the LA (effective pulmonary blood flow) due to reduced ventricular and vascular compliance of the systemic circuit [26]. Respiratory variation also effects shunting across the atrial communication.

When a PDA is also present, flow across the PDA is dependent on the size of the inter-atrial communication and the PVR. With a non-restrictive ASD and a low PVR, blood flows from the aorta to the PA across the PDA (effective pulmonary blood flow) and left to right across the ASD (effective systemic blood flow).

As the PVR increases, shunting across the PDA and ASD becomes bidirectional. A unique clinical scenario occurs when raised PVR results in the PAP exceeding aortic pressure, causing blood to shunt across the PDA from the PA to the descending aorta, creating a reverse differential cyanosis. In this scenario, post ductal saturations (lower limb) will be higher than preductal (right hand). This phenomenon only occurs in TGA with preductal coarctation/interruption or when PVR is elevated (usually due to persistent pulmonary hypertension). A restrictive ASD or small PFO can cause elevated PVR due to raised LAP, resulting in poor mixing and severe cyanosis. The PFO may even close due to the raised LAP – eliminating a source of atrial mixing. Smaller infants with inadequate atrial mixing are at a high risk of preoperative or sudden death at birth due to PFO closure [27]. A BAS may be lifesaving in this setting.

TGA with ventricular septal defect

Although VSDs occur in 40% of patients with TGA, approximately one-third of these are too small and not functionally significant [28]. In TGA with non-restrictive VSDs, mixing at the VSD is usually less efficient than at the atrial level. This is due to larger pressure gradients throughout the cardiac cycle at the level of the ventricles which typically shunt blood in one direction, in this case from right to left (effective pulmonary blood flow). Flow across the PDA is also predominantly effective pulmonary blood flow, with blood shunting from the RV to the aorta to the PA. Effective systemic blood flow originates from blood shunted from left to right across an ASD or PFO. The increased pulmonary blood flow will pass almost entirely through the LV, resulting in a volume-overloaded LV and subsequent heart failure. This increased pulmonary blood flow, particularly in patients with a VSD, significantly increases the risk of developing PAH, as systemic pressures are transmitted to the pulmonary vasculature.

TGA with left ventricular outflow tract obstruction

TGA with LVOTO occurs in approximately 5–10% of patients with TGA and is more commonly associated with a VSD. In TGA with LVOTO and VSD, there is a large anatomical left to right shunt and reduced pulmonary blood flow. Effective pulmonary blood flow is carried via the PDA. Due to a low Qp, LA hypertension and cardiac failure do not occur, but severe systemic hypoxemia is present. Cyanosis after birth is a common clinical feature, the degree of which is dependent on the magnitude of the obstruction.

Dynamic LVOTO can occur in patients with TGA/IVS who do not undergo an early ASO. This happens when the LV pressure drops below the RV pressure in the postnatal period due to a corresponding drop in PVR. High systemic right ventricular pressure displaces the interventricular septum posteriorly into the left ventricular outflow tract during systole. Dynamic LVOTO should be resolved after ASO; however, if left untreated, this obstruction can become fixed over time necessitating alternative surgical strategies.

Fixed LVOTO requires detailed surgical planning with assessment of the degree of LVOTO and adequacy of the pulmonary valve. Selected patients with fixed LVOTO may still proceed to ASO with satisfactory short- and mid-term results [29, 30]. Neo-aortic valve regurgitation remains a concern in long term [29]. If LVOTO is severe and fixed, other surgical options than ASO are advised [29, 30].

TGA with right ventricular outflow tract obstruction

Obstruction to the systemic circulation is an infrequent but important variant of TGA and occurs in approximately 5–10% of cases [31]. Systemic saturations will be variable depending on the degree of RVOTO and significant systemic hypoperfusion may occur due to impedance of systemic blood flow (including absent or diminished femoral pulses) if the PDA becomes restrictive. As mentioned above, a finding of reverse differential cyanosis indicates significant anatomical left-to-right shunting at the PDA and should alert clinical suspicion of coarctation of the aorta. A detailed evaluation of the aortic arch anatomy and of any coarctation and/or aortic arch hypoplasia are important surgical considerations.

KEY POINTS: NATURAL HISTORYAND PATHOPHYSIOLOGY

- In d-TGA the pulmonary and systemic circulations exist in parallel.
- Deoxygenated venous blood recirculates to the body through the right side of the heart, without being oxygenated in the lungs, and oxygenated blood recirculates between the lungs and the left side of the heart.
- Intercirculatory mixing is vital for survival in children with d-TGA.
- Mixing can occur through a PFO, ASD, VSD, or PDA.
- Atrial level mixing is the most effective way to increase oxygenation.
- Without treatment, death from hypoxia and congestive heart failure will occur in 90% of patients within the first year of life.

Clinical presentation and diagnostic features

With the evolution of fetal echocardiography, most diagnoses of TGA are likely to occur antenatally. As a result, a preliminary management plan can be formed aimed at postnatal stabilization before a more definitive surgical correction takes place. Antenatal diagnosis facilitates planned delivery and early administration of prostaglandin preventing the production of lactate and thus improving the neonates' preoperative condition. In addition, it reduces the risk of cerebral damage which has been shown to correlate with high lactates [32]. A detailed echocardiogram is repeated at birth which allows for comprehensive assessment of cardiac anatomy and the associated anatomical defects and to aid preoperative management and surgical planning. The echo must be performed promptly as prolonged duration of severe cyanosis and tissue hypoxia are important factors in determining acidosis, ventricular function, and ultimately multiple organ failure.

Clinical features in TGA are difficult to distinguish from other causes of neonatal cyanosis:

- **Cyanosis**-The degree of cyanosis is determined by the amount of intercirculatory mixing. In infants with mild cyanosis, the lesion may only be detected on the basis of a pulse oximetry screen.

  TGA/IVS: If the ASD is restrictive, limited intercirculatory mixing occurs leading to profound central cyanosis and tachypnea presenting within the first few hours of life. Arterial oxygen saturation will usually range between 50 and 70% unresponsive to oxygen administration.

  TGA LVOTO: Due to reduced pulmonary blood flow from LVOTO or pulmonary obstructive disease, these patients can present with significant cyanosis. Reverse differential cyanosis might be present.

  TGA/VSD: In infants with a large VSD that allows for satisfactory mixing between the two circulations, cyanosis may only be perceived during episodes of crying or agitation. However, signs of congestive heart failure will prevail due to ventricular overload: tachypnea, tachycardia, failure to thrive, a gallop rhythm, and eventually hepatomegaly. Arterial oxygen saturations will range between 75 and 90%.
- **Tachypnea** – Patients will usually have a respiratory rate of over 60 breaths per minute and appear comfortable without other signs of respiratory distress (grunting, nasal flaring, subcoastal, or tracheal recession). Infants with large VSDs may present with severe respiratory distress due to heart failure by three to 4 weeks of age.
- **Heart murmurs** – Heart murmurs are not a consistent finding in patients with TGA. An ejection systolic murmur is associated with left outflow tract obstruction (i.e., PS). A pansystolic murmur may be heard with a small to moderate VSD or PDA.
- **Diminished pulses** – Diminished femoral pulses may be seen in patients who also have coarctation of the aorta or interruption of the aortic arch.

Cardiac catheterization is not routinely performed unless it is in conjunction with BAS, when ECHO cannot establish coronary artery anatomy, or to quantify pulmonary vascular occlusive disease and PVR in the older child. Table 29.2 presents common ECG and chest radiograph findings in the various TGA morphologies.

Table 29.2 ECG and Chest Radiograph (CXR) findings in various D-TGA morphologies

TGA morphology	ECG	CXR
TGA IVS	Essentially normal	"Egg on side"
TGA VSD	Normal or RVH	Narrow superior mediastinal area, cardiomegaly, prominent vascular markings
TGA LVOTO	Normal or biventricular hypertrophy	Cardiomegaly, increased pulmonary vascular markings

Preoperative management

After birth, infants with TGA require early treatment; it is therefore recommended that they are delivered at or close to a tertiary care hospital that provides pediatric cardiology and cardiac surgery facilities [33]. Enabling early stabilization and optimization of these children can reduce cost and transport-related complications [34]. Infants born outside of a tertiary center will need to be stabilized in NICU prior to transfer; some institutions will electively intubate these patients, although there is increasing evidence that rates of complications are higher in intubated neonates [35].

The initial management of newborns with TGA should focus on stabilization, optimization of the mixing of systemic and pulmonary circulations, oxygen delivery, maintenance of adequate systemic perfusion and correction of acidosis. To ensure sufficient mixing between the two parallel circulations, an intravenous infusion of prostaglandin E1 is recommended to maintain patency of the PDA until a comprehensive series of post-natal echocardiograms has

been completed to assess all sites of possible intercirculatory mixing. Prostaglandin infusions should be started at 0.05 mcg/kg/min, higher doses may be necessary to reopen a closed PDA. Prostaglandin may cause fever, platelet dysfunction, hypotension and apnea, particularly with increased doses which may necessitate intubation. If PGE1 does not improve tissue oxygenation, then an urgent balloon atrial septostomy (BAS) should be performed as ductal shunting is often insufficient in the presence of a restrictive ASD.

Transcatheter approaches

A BAS can be performed in a catheterization lab under angiography or in NICU using echocardiography. Occasionally, BAS may be performed at the local hospital by a specialist cardiac retrieval team so that the patient can be stabilized prior to transport to the cardiac center for definitive surgery. Because BAS can be safely performed under echocardiographic guidance, preoperative diagnostic cardiac catheterization should be considered only in selected cases for diagnosis of complex lesions or if institutional experience does not permit performance of atrial septostomy under echocardiographic guidance. Exact coronary artery definition is generally not required by the majority of surgeons as it can be determined in the operating room, and ASO is performed for almost every coronary artery arrangement.

During BAS, a balloon is passed via the umbilical vein or the femoral vein, into the left atrium across the PFO, the balloon is inflated and pulled back briskly across the septum, to tear the inferior aspect of the foramen ovale (Figure 29.7). This is repeated at least once to ensure adequate enlargement of the ASD; echocardiogram is performed to assess the intercirculatory mixing.

Outcomes from balloon atrial septostomy

The introduction of balloon atrial septostomy (BAS) by Rashkind and Miller in 1966 has greatly improved the prognosis of patients with TGA, with 3-month survival increasing from 20 to 85% [37]. The significant improvement in saturations must be weighed against the risk of vascular trauma, arrhythmias, and rare complications such as atrial perforation and avulsion of the inferior vena cava [38]. Mortality of an urgent BAS is around 3%, with increased risk of complications if performed out of hours [39]. Although there is no increased mortality between patients who received a BAS and patients who did not, some studies have shown a strong association between BAS and preoperative stroke in neonates with TGA [39, 40]. Multiple studies have described MRI changes in both white and grey matter locations, including focal ischemic changes and periventricular leukomalacia (PVL) in patients with TGA, with reported prevalence rates of 30% [41]. Although it is possible that this is due to embolic phenomenon from the BAS, there are likely to be multifactorial components, including the degree of hypoxemia and hemodynamic instability. Multiple papers have now refuted the association between BAS and stroke [42, 43].

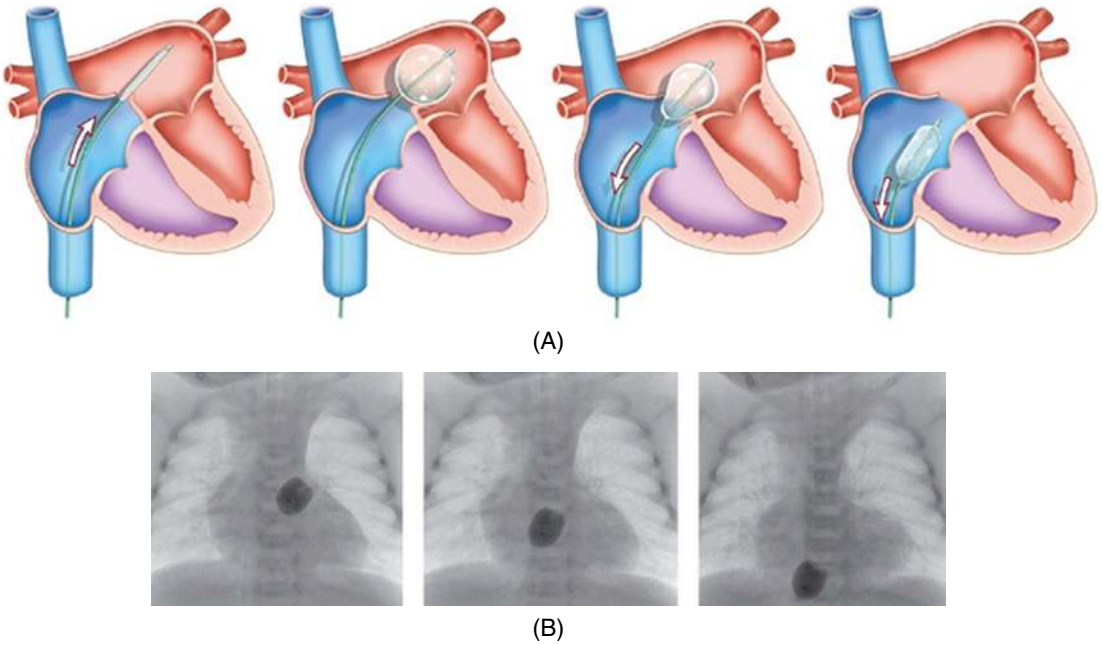


Figure 29.7 Balloon atrial septostomy. (A) Schematic representation of the maneuver. A balloon-tipped catheter is introduced via the inferior vena cava into the right atrium. After passing through the foramen ovale, the balloon is inflated into the left atrium and then pulled across the septum to enlarge the opening. Finally, the balloon is rapidly deflated, and the catheter removed. (B) Angiographic images showing the different steps of the maneuver. (Source: Seguela et al. [36]. Reproduced with permission of Elsevier.)

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Anesthesia for balloon atrial septostomy

A BAS can be performed in the cardiac catheterization laboratory under angiographic guidance or in the neonatal intensive care unit under echo guidance, with the latter being more common.

The procedure is performed by a pediatric interventional cardiologist, with a neonatologist or an anesthetist present to manage sedation and mechanical ventilation.

A stable airway must be guaranteed, although not all neonates need to be intubated. Our center advocates routine intubation, this permits optimal sedation and analgesia, as well as permitting the use of paralysis to facilitate BAS. Prior to the procedure, an ABG, baseline blood tests, and IV access are required. A unit of red blood cells is essential and ideally crossmatched if time permits. Baseline observations including HR, RR, pre- and post-ductal saturations, BP, blood glucose, and urine output should be documented prior to and throughout the procedure.

Intubated neonates will usually be sedated with a morphine infusion, with additional boluses of fentanyl, ketamine or midazolam given as required. In spontaneous ventilating neonates, small incremental boluses of appropriate sedation should be used, including opioids (morphine or fentanyl), midazolam, and ketamine [44]. Dexmedetomidine is a safe drug in children with congenital heart disease with no significant respiratory depressive effect; thus, it may be useful in this setting [45]. Acetaminophen can be a useful adjunct in these patients.

If a BAS is performed successfully, systemic oxygen saturations should begin to increase immediately; if adequate mixing is seen at the atrial level, then the PGE1 infusion can be gradually discontinued (as long as there are no concerns regarding aortic arch obstruction). The aim is now to ensure hemodynamic stability and optimize preoperative condition. Once the patient is stable, they can be fed, and all further required investigations should be performed.

Associated medical problems (such as respiratory distress, necrotizing enterocolitis (NEC), and intracranial hemorrhage) should be diagnosed and treated appropriately. If the patient is extremely premature or other associated conditions are present, an early ASO should be postponed. If intracranial hemorrhage occurs, surgical repair is usually delayed by 2 weeks. Due to this delay, the left ventricular mass will decrease and will need to be "re-trained" to support a high SVR after the ASO (see below).

A small proportion of patients may remain cyanotic after a BAS, requiring further detailed echocardiography to confirm the ASD is unrestrictive, assess the patency of the PDA, and assess for pulmonary hypertension if present. Incidence of persistent pulmonary hypertension in neonates with TGA is 12.5%, occurring more commonly in patients with TGA /IVS [46]. Multiple treatment strategies have been used with variable success, including sedation, paralysis and hyperventilation, inhaled nitric oxide (NO) [47], sildenafil, bosentan [48], and extracorporeal life support (ECLS) [49]. The prognosis in these patients remains poor [50].

KEY POINTS: PREOPERATIVE MANAGEMENT

- The initial management of newborns with TGA should focus on stabilization and optimization of the mixing of systemic and pulmonary circulations.
- To ensure sufficient intercirculatory mixing, an intravenous infusion of prostaglandin E1 is required to maintain patency of the PDA.
- An urgent balloon atrial septostomy (BAS) may be required to improve intercirculatory mixing in patients with severe hypoxemia.
- A BAS can be performed in the cardiac catheterization laboratory under angiographic guidance or in the neonatal intensive care unit under echo guidance.
- Mortality of an urgent BAS is 3%.

Surgical options

The ASO, first performed successfully in 1975 by Adib Jatene, has become the standard corrective procedure for patients with D-TGA and has revolutionized their survival (Figure 29.8). Mortality has decreased from >90% to <1% in patients with simple TGA and 4% with complex TGA [51]. The ASO has been used as the preferred procedure for patients with D-TGA since the late 1980s and has replaced the earlier atrial switch techniques by Mustard and Senning.

Indication and timing of ASO

Significant uncertainty exists regarding the optimal timing of surgical repair. For ASO to be successful, the LV must have significant myocardial mass to support the systemic circulation. At birth, the LV mass is equal to that of the RV. In TGA/IVS, as the PVR drops postnatally the left ventricle involutes, losing muscle mass and thus becoming unable to support the systemic circulation [52]. Due to this, the majority of ASOs for TGA/IVS are performed within the first 2 weeks of life [53]. In older infants with TGA/IVS, there is a concern that the LV will decondition and therefore fail when exposed to higher systemic pressures after ASO, resulting in low cardiac output syndrome. There is no clear upper age limit for ASO, with most surgeons performing a primary ASO up to 4 weeks of age (Box 29.1). Beyond 4 weeks, a primary ASO becomes controversial, and it is likely that patients will require post-op mechanical circulatory support and a prolonged ICU admission [54]. A study from Lo Rito et al, however, has suggested that primary ASO can be safely performed in TGA/IVS patients who present late with a severely deconditioned LV. They showed no significant differences in early mortality or LV recovery, although an increase in neurological injury was noted, which was thought to be due to the 3- to 5-fold increase in ECMO use [55]. For infants >2 months old, a rapid two stage ASO is recommended. A two-stage ASO involves pulmonary artery banding (+/− an aortopulmonary shunt in cyanotic patients) to "re-train" the left ventricle by inducing LV hypertrophy before performing an ASO within 2 weeks. The PA band must be sufficiently tight to increase pressure in the LV to approximately one-half to two-thirds of the systemic ventricle without compromising pulmonary blood flow.

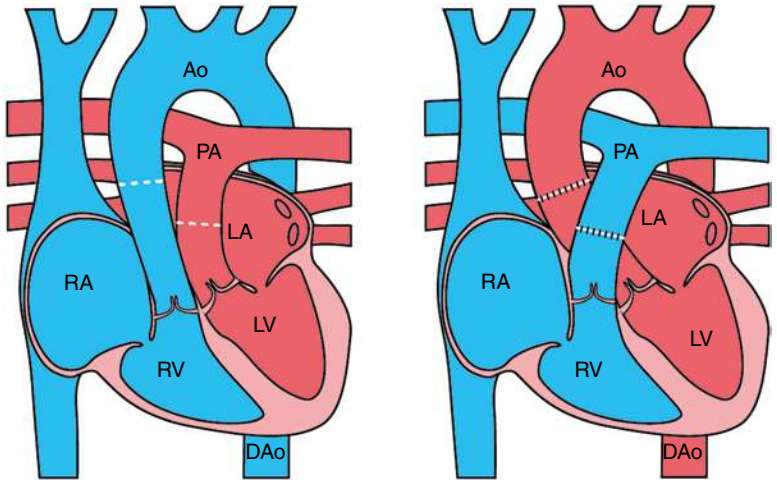


Figure 29.8 The arterial switch operation (ASO). Schematic representation of d-transposition of the great arteries anatomy before (A) and after (B) the ASO. Ao, aorta; PA, pulmonary artery; LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle.

Box 29.1: Indications for LV retraining prior to ASO [56]

- >3 weeks old
- <35 g/m^2
- Banana-shaped IVS (IVS bulges right to left due to low LV pressure)
- Absence of PDA or LVOTO

The majority of the left ventricular mass increase occurs in the first seven days after banding, with the ASO therefore typically performed within a week [57]. Although primary ASOs have better outcomes, a rapid two-stage repair may be unavoidable in patients where a primary ASO would expose the infant to excessive risk. Primary ASO may not be possible due to prematurity, sepsis (e.g., NEC), low birth weight (<1.5 kg) or late presentation.

Timing of surgery may also have an impact on neurodevelopmental outcome with some evidence to suggest that delaying surgery beyond 2 weeks of age is associated with impaired brain growth and slower language development at 18 months of age [58]. This may be due to the effects of prolonged hypoxia on the developing brain, with the risk of PVL increasing with lower arterial oxygenation and longer time to surgical repair [43].

Some evidence supports day 3 of life as the optimal time for an ASO, with increasing morbidity and healthcare cost beyond this timeframe. Currently, in Europe, 30% of ASOs are performed within the first week of life [59], with the majority of ASOs performed on Day 6 or 7 in the United States [60]. Preliminary reports have shown that performing an ASO in the first few hours of life is safe, thus avoiding the need for a BAS and theoretically reducing neurological impacts of prolonged hypoxia. This technique remains very controversial having been carried out in a limited number of cases [61, 62].

In the subsets of patients where the LV is exposed to systemic pressures (such as LVOTO, a large VSD, or PDA), LV mass is maintained after birth, preventing ventricular deconditioning beyond the age of 2–3 weeks. In these patients, there is less urgency to perform the surgery, and it can be done up to 6 weeks of life. In reality, they are usually operated on within the first month, before intractable cardiac failure or pulmonary vascular occlusive disease can occur.

TGA with left ventricular outflow tract obstruction

Surgical intervention in TGA with LVOTO varies with the type of LVOTO obstruction. Dynamic LVOTO obstruction is amenable to ASO as the dynamic nature of the LVOTO will be fully reversed, with no residual LVOT gradient.

Challenging decision-making is required in TGA with mechanical LVOT obstruction. The surgical decision is dependent on the complexity of LVOT obstruction, the size of the pulmonary valve, and the size of the VSD (Figure 29.9). ASO and muscle resection may be possible in certain patients with a normally aligned LVOT where complete or near complete relief of the LVOTO is to be expected. There is an increased risk of reintervention of the LVOT or neo-aortic valve [30]. For complex TGA with severe or fixed LVOTO (due to subvalvular, valvular or multilevel obstruction) and a VSD, an ASO is generally not performed. There are three main surgical options: the Rastelli, the REV and the Nikaidoh procedure (see below).

Aortic arch obstruction (coarctation with hypoplastic arch or interruption) is present in only 5–9% of TGA patients, but it is much more frequent in patients with TBA (more than 50%). Previously a two-stage repair was advocated in these patients that included a primary coarctation reconstruction +/− PA band, followed by an ASO or intracardiac repair months later; however, mortality rates were high. Now a one-stage ASO is usually undertaken [63].

Arterial switch operation

The ASO is performed through a median sternotomy on cardiopulmonary bypass (CPB). Both of the great vessels are transected distal to their respective valves, translocated, and

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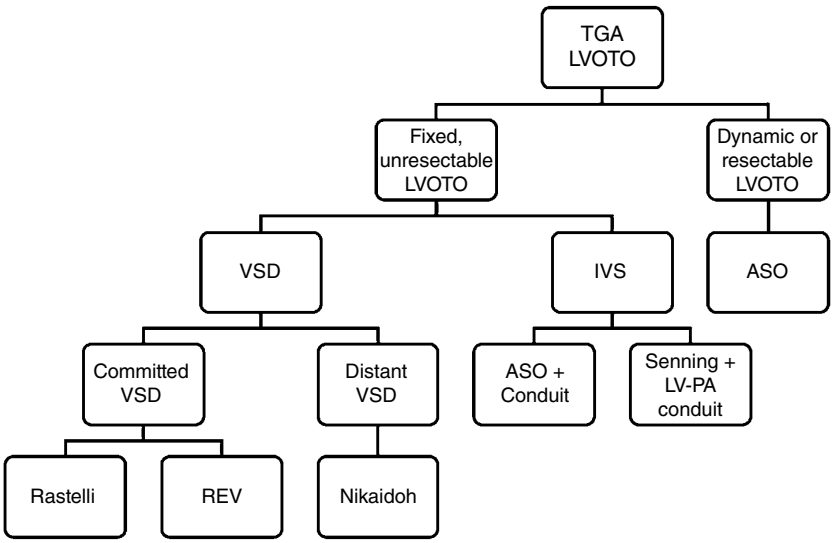


Figure 29.9 Flowchart illustrating anatomical factors determining surgical decision-making in patients with transposition of the great arteries (TGA) with left ventricular outflow tract obstruction (LVOTO). VSD, ventricular septal defect; IVS, intraventricular septum; ASO, arterial switch operation; LV-PA conduit, left ventricle to pulmonary artery conduit; REV, Réparation à l'Etage Ventriculaire.

re-attached to the opposite root. This will result in the right ventricle attaching to the pulmonary artery and the left ventricle to the aorta. When CPB is established, the ductus arteriosus is divided, the ascending aorta is clamped, and cardioplegia is administered. The ascending aorta is transected above the commissures and the left and right coronary arteries are excised with 3–4 mm of the surrounding tissue. These aortic explant sites are repaired with a pericardial patch. The main pulmonary artery is transected, and the coronary arteries are reimplanted into the remaining root of the PA which will become the neo-aorta (Figure 29.10). This clarifies why delineating coronary artery anatomy is important prior to surgical repair. The LeCompte maneuver (Figure 29.11) is then performed; this involves the PA being brought anterior to the aorta before it is re-anastomosed to the native aortic root whilst the distal aorta is re-anastomosed to the proximal cuff of the native pulmonary artery (now the neo-aorta). This results in the aorta lying behind the bifurcation of the PA, which reduces the risk of subsequent PA stenosis.

An ASD is usually closed by direct suture, while patients with a VSD require a pericardial patch. In children with TBA, the VSD is closed with a patch placed diagonally to achieve continuity of the LV with the neo-aorta, while the neo-PA remains connected to the RV.

Once the aortic cross-clamp is removed, the myocardium is carefully observed for perfusion, and ECG and LAP are closely monitored. Ischemia of the myocardium is reflected by lack of reactive hyperemia or a rise in LAP, even before the ECG changes become apparent. A rise of LAP above 10 mmHg requires careful re-examination of the myocardium and coronary vessels to ensure adequate coronary flow. During rewarming, the aortic sinus defect is repaired, the anastomosis is completed, and temporary atrial and ventricular pacing wires are placed (Figure 29.12).

Other surgical procedures

Rastelli procedure

The Rastelli procedure is used to anatomically correct TGA with VSD and fixed LVOTO. A right ventriculotomy is performed, and a patch is placed to diagonally direct blood from the LV through the VSD toward the aorta. The PA is ligated at the level of the pulmonary valve, and a valved RV-to-PA conduit is placed [65]. The conduit can be an aortic or pulmonary homograft with a polytetrafluoroethylene graft extension. This achieves the LV to the aorta and the RV to the PA continuity, whilst bypassing the LVOTO (Figure 29.13). It is advantageous as it allows the LV to act as the systemic ventricle. The Rastelli procedure requires a large subaortic VSD, although restrictive VSDs can be enlarged to allow precise patch placement. Enlargement of the VSD has been shown to reduce the risk of developing post-operative LVOTO but may increase the risk of heart block from damage to the conduction pathway [66].

In patients with severe LVOTO, where the pulmonary blood flow is low and inter-arterial mixing is limited, a systemic-to-pulmonary shunt (usually a modified Blalock– Taussig shunt) is inserted in the neonatal period; these children are too young to be considered for a primary Rastelli procedure. This is used to increase pulmonary blood flow until the child has outgrown the BT shunt and a Rastelli operation will then be performed. This usually occurs before two years of age.

Senning and mustard procedures

The first surgical treatments of TGA were the atrial switch operations, performed by Senning and Mustard for the first time in 1958 and 1964, respectively. Senning and Mustard procedures (also known as atrial switch procedures) provide physiological, but not anatomic correction of the TGA. During the Senning procedure, an autologous tissue from the right atrial wall and intra-atrial septum is used to create an

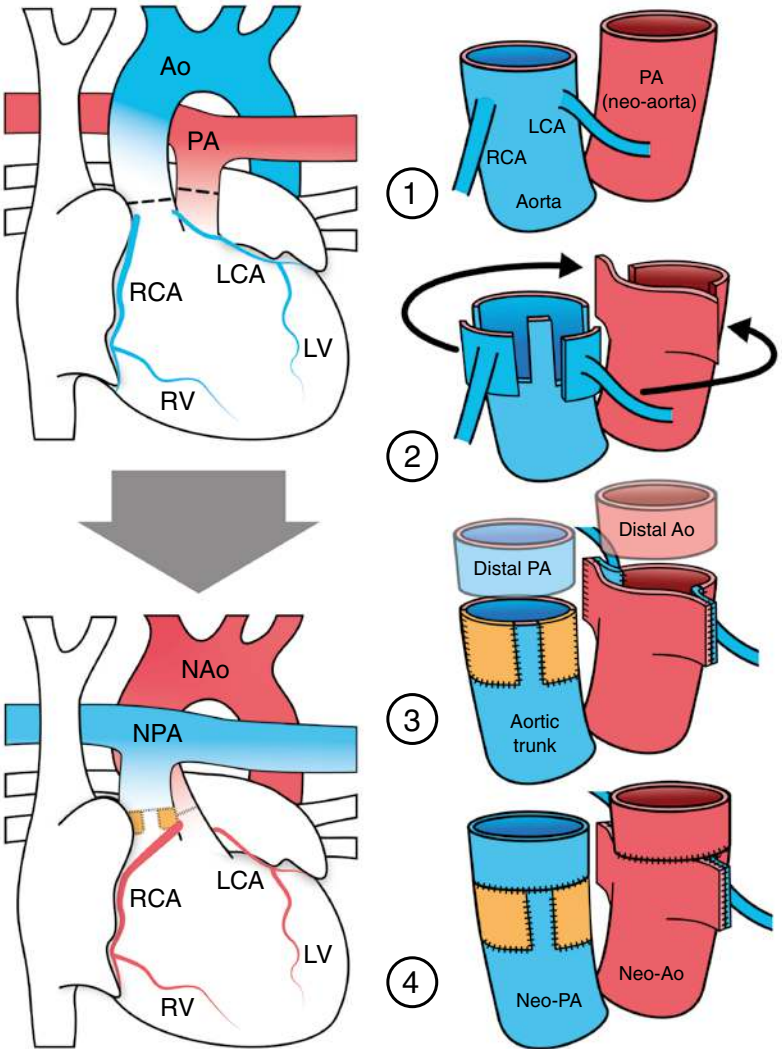


Figure 29.10 Technique for the arterial switch operation. (1) The great arteries are transected above the sinuses of Valsalva. (2) The coronary arteries are excised from the aorta, transposed posteriorly, and reanastomosed to the pulmonary artery trunk: the neo-aorta. (3) The distal aorta is brought behind the pulmonary artery (LeCompte maneuver) and anastomosed to the neoaorta. (4) Completed repair. Ao, aorta; PA, pulmonary artery; LCA, left coronary artery; RCA, right coronary artery; RV, right ventricle; LV, left ventricle; NPA, neo-pulmonary artery; NAo, neo-aorta.

intracardiac baffle redirecting systemic venous blood via the mitral valve to the LV and pulmonary venous blood via the tricuspid valve to the RV [67]. The Mustard procedure was developed as a modification of the Senning technique, where the interatrial septum is excised to create a large ASD and a baffle, made of either autologous pericardium or a synthetic material, redirects systemic and pulmonary venous blood flow to the LV and RV, respectively (Figures 29.14 and 29.15). Despite the Mustard procedure being a simplified technique, many deem the Senning procedure to be superior due its use of an autologous atrial tissue, thus allowing atrial growth and preserving contractility.

Réparation à l'Etage Ventriculaire (REV) and Nikaidoh procedures

Réparation à l'Etage Ventriculaire (REV) involves radical excision of the outlet septum to enlarge the VSD, then a patch closure to direct the LV flow to the aorta. The PA is transected with the distal end brought anterior to the aorta (LeCompte) and the proximal stump ligated. The distal PA is then augmented with an autologous patch and anastomosed directly to the RV creating RV-PA continuity [69] (Figure 29.16). REV avoids the use of an extra-cardiac prosthetic conduit and reduces the risk of intracardiac tunnel obstruction. It is feasible in patients with anatomic contraindications to the Rastelli operation, and it may reduce the need for re-operation and prevalence of residual pulmonary outflow tract obstruction. Disadvantages are the lifelong implications of pulmonary regurgitation and tension of the pulmonary artery reconstruction leading to early RVOTO [71].

During the Nikaidoh procedure, the aortic root is completely mobilized and translocated posteriorly to overlie the LV. The VSD is closed, and the PA is translocated anteriorly (LeCompte) and anastomosed to the RV using an autologous pericardial patch to reconstruct the RVOT (Figure 29.17). Patients with a hypoplastic right ventricle benefit the most from the Nikaidoh procedure. It creates a more normally

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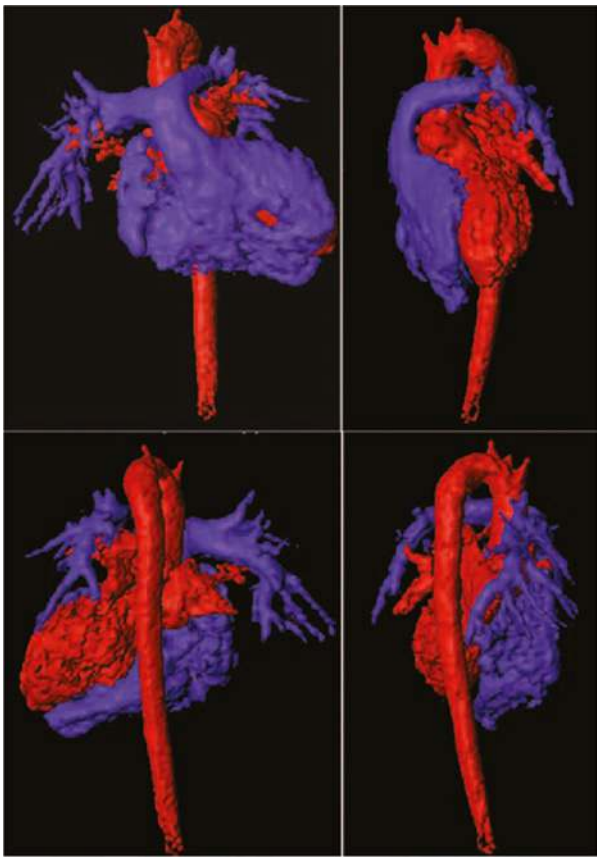


Figure 29.11 Three-dimensional gadolinium-enhanced magnetic resonance angiography in a patient with transposition of the great arteries showing the bifurcation of the pulmonary arteries arising from the right ventricle (blue) in front of the aorta arising from the left ventricle (red) after arterial switch operation with the LeCompte procedure. (Source: Voges et al. [64]. Reproduced with permission of Wolters Kluwer Health, Inc.)

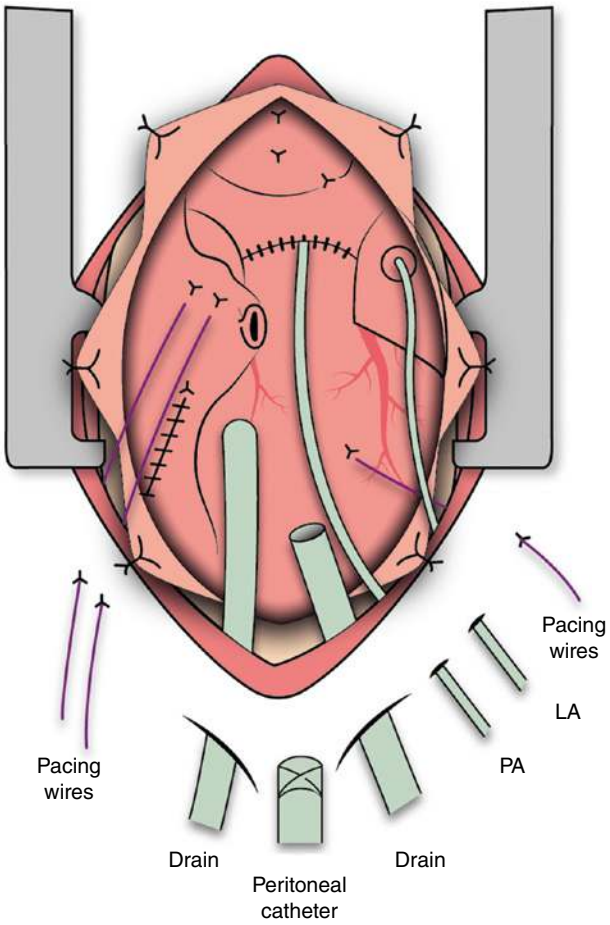


Figure 29.12 Layout of the chest before sternotomy closure in the arterial switch operation. PA, pulmonary artery catheter; LA, left atrial catheter.

aligned right and left outflow tracts, reducing the risk of recurrent LVOT obstruction and RV-PA compression by the sternum.

Outcomes for ASO

Long-term outcomes after ASO are excellent, with over 95% survival at 25 years after discharge [72]. ASO also provides very good functional status and little limitation in physical activity, with over 95% of patients in NYHA functional class I [51]. These outcomes are particularly favorable in comparison to atrial switch operations, Mustard or Senning, where long-term survival is 80% at 20 years and 75% at 25 years respectively [73]. Despite excellent survival, patients are at risk for morbidity that may require further surgical intervention into adulthood (Table 29.3). Overall freedom from catheter or surgical re-intervention is 75% at 20 years, with re-intervention being significantly more common in the TGA/VSD cohort post ASO [75, 76]. The most common reason for re- intervention post ASO is pulmonary artery stenosis, possibly due to inadequate growth at the neo-pulmonary anastomotic site [76]. Performing ASOs in the neonatal period reduces the need for a PA band, which, alongside the introduction of the LeCompte maneuver, has likely reduced the incidence of PA stenosis, resulting in <5% now requiring reintervention [51, 77, 78].

Coronary artery insufficiency has been a long-held concern after ASO and led to high early hospital mortality when ASO was first introduced. As surgical techniques and experience have improved, early mortality from coronary artery complications has dropped significantly. Coronary artery complications are the primary cause of early mortality with ischemia or ventricular dysfunction most commonly presenting in the first 3 months postoperatively [79]. This is likely due to anatomical kinking, torsion, or external compression, thus reducing coronary perfusion. Long-term outcomes are also dependent on the patency of the coronary arteries, although late deaths due to coronary insufficiency are rare. It is thought that late coronary artery insufficiency is caused by stretching of the coronary arteries as they grow or progressive fibrocellular intimal thickening [80]. This may also predispose to early atherosclerotic disease, which is screened for during long-term follow up. Coronary lesions occur in around 3 to 6.8% of patients, with coronary angiography being the gold standard as lesions are often subclinical [75, 79, 81]. This may be due to collateral circulation, which may mask ischemia on noninvasive screening modalities (ECG, echocardiography, stress tests, etc.) [79].

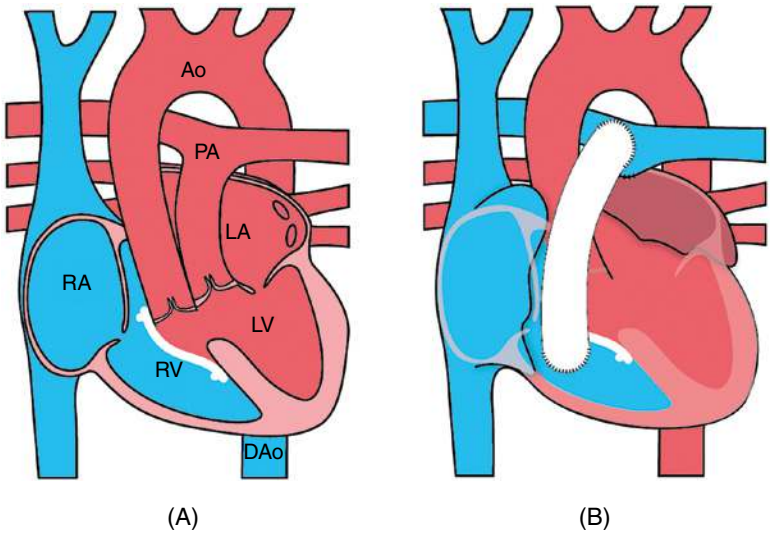


Figure 29.13 Rastelli procedure for repair of transposition of the great arteries with ventricular septal defect (VSD) and left ventricular outflow tract obstruction (LVOTO). (A) Baffle closure of the VSD with a patch redirecting left ventricular outflow across the aortic valve. (B) In the presence of LVOTO, the proximal pulmonary artery (PA) is ligated, and a valved conduit is placed from the RV to the main PA. Ao, aorta; PA, pulmonary artery; RA, aright atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; DAo, descending aorta.

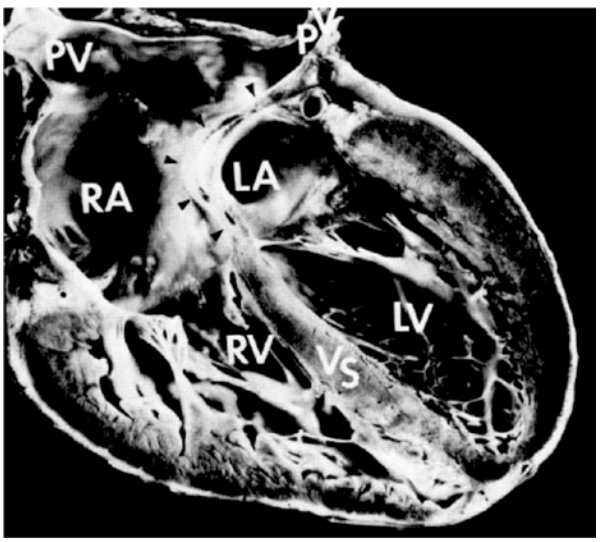


Figure 29.14 Postoperative specimen of transposition of the great arteries after the Mustard operation. The tomographic cut is comparable to an apical four-chamber echocardiographic projection. The patch within the atrium (black arrowheads) directs pulmonary venous blood to the tricuspid valve and into the right ventricle (RV). LA, left atrium; PV, pulmonary vein; RA, right atrium; VS, ventricular septum. (Source: Warnes [68]. Reproduced with permission of Wolters Kluwer Health, Inc.)

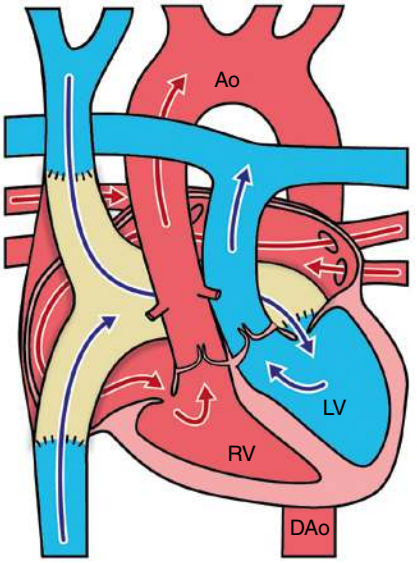


Figure 29.15 The Mustard procedure. An intra-atrial baffle diverts blood from both the superior vena cava (SVC) and the inferior vena cava (IVC) across to the mitral valve and left ventricle, which ejects blood to the pulmonary artery. Pulmonary venous blood is returned via the tricuspid valve and RV, which ejects blood into the aorta. The baffle is made from pericardium or a synthetic material. Ao, aorta; RV, right ventricle; LV, left ventricle; DAo, descending aorta.

In the immediate post-op period after ASO, there is a high incidence of chronotropic impairment due to sympathetic denervation, despite this over 96% of patients are in sinus rhythm [51, 79]. Arrythmias present after the immediate post-op period require urgent investigation to rule out coronary artery abnormalities or residual lesions resulting in hemodynamic compromise. Late arrythmias are a relative frequent complication occurring in around 2 to 10% of patients [51, 79, 82, 83].

Neo-aortic valve regurgitation is a frequent finding after ASO as the native pulmonary valve is exposed to systemic pressures. Up to 20% of patients develop some degree of aortic regurgitation, with 5% of patients requiring neo-aortic root or valve reoperation at 20 years, increasing to 8% at 25 years. This demonstrates the significant attrition of the neo-aortic valve over time and the need for ongoing close surveillance of ASO survivors. It is not yet known how well the

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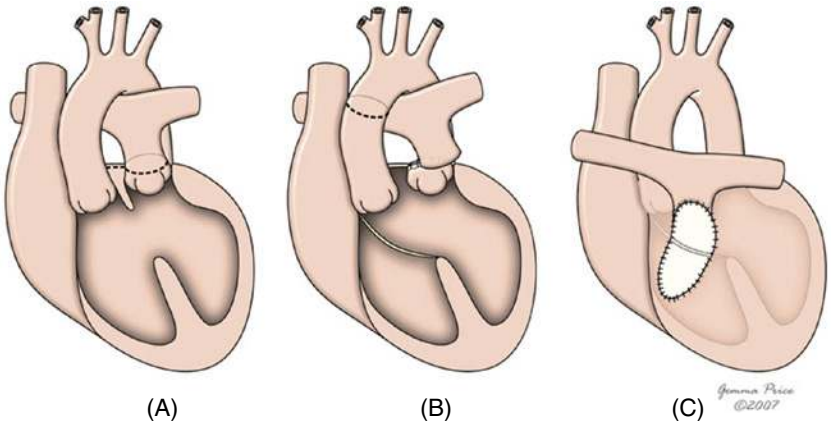


Figure 29.16 This figure shows the innovations of the REV procedure relative to the Rastelli procedure, (A) preoperative anatomy, with resection of the muscular outlet septum (B) and use of LeCompte maneuver (C) which avoids the use of an extacardiac conduit. (Source: Martins et al. [70]. Reproduced with permission of Cambridge University Press.)

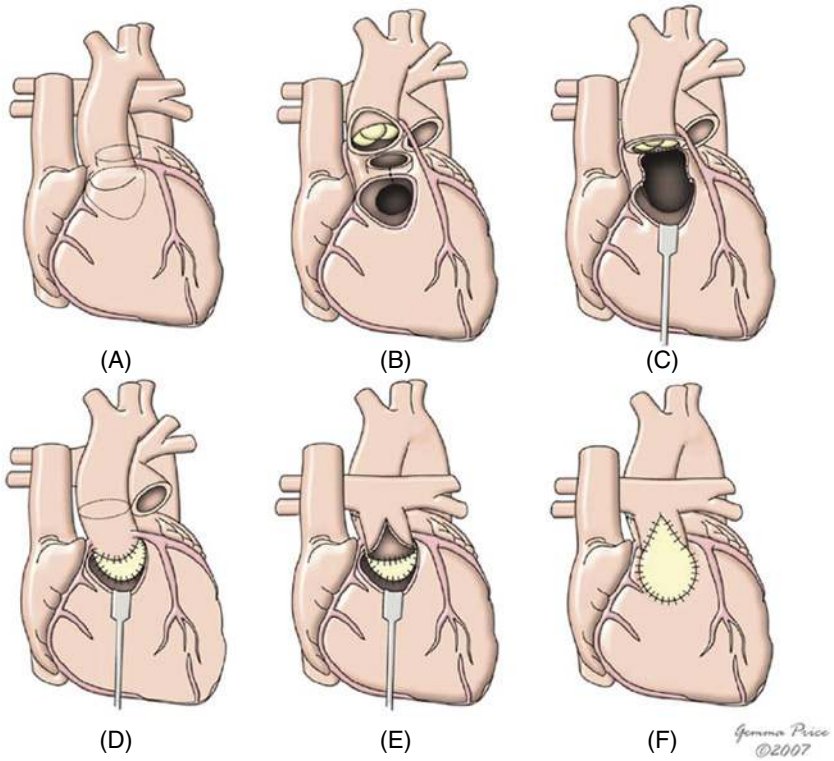


Figure 29.17 The illustration shows the major steps of Nikaidoh's procedure. (A) Shows the areas for harvesting the aortic root and transection of the pulmonary trunk. In (B), the aorta and pulmonary trunk have already been disconnected from their previous insertion, and the line of division of the outlet septum is shown. (C and D) show aortic translocation and reconstruction of the left outflow tract, with a pericardial patch used to close the ventricular septal defect. In (E) and (F), the pulmonary trunk is sutured to the right ventricular outflow tract, and the reconstruction is completed with a pericardial patch. (Source: Martins et al. [70]. Reproduced with permission of Cambridge University Press.)

neo-aortic root will cope with systemic pressure as these patients reach middle age [84, 85].

With increased survival after TGA repair, attention has turned toward quality of life and functional outcomes. There is increasing evidence that neurodevelopmental impairment is more prevalent in children after TGA repair than in the general population [86]. Neurodevelopmental impairment in these children ranges from motor delay, cognitive impairment, poorer academic achievements, speech and language dysfunction and psychosocial impairment. Multiple studies have described MRI changes in both white and grey matter locations, including focal ischemic changes and PVL in patients with TGA, with reported prevalence rates of 30% [41]. However, MRI abnormalities poorly predict adverse neurodevelopmental outcomes in these patients [58]. Poorer neurodevelopmental outcomes are likely to be

Table 29.3 Postoperative sequelae following the arterial switch operation

Postoperative sequalae	Incidence
Supravalvar pulmonary stenosis[a]	~10%
Supravalvar aortic stenosis[a]	<5%
Neoaortic root dilatation	Essentially 100%
Neoaortic regurgitation	~50%[b]
Significant arrythmia	Rare
Asymptomatic coronary occlusion	2–3%
Pulmonary hypertension	Rare
Hypertrophied bronchial collaterals[a]	<5%
Abnormal bronchial collaterals[a]	Unknown
Sudden death	Rare

[a] Requiring intervention.

[b] Increase with increasing duration of follow-up.

Source: Wernovsky et al. [74]. Reproduced with permission of John Wiley & Sons.

multifactorial and strongly associated with the infant's prenatal, neonatal, and perioperative course. Risk factors include post-natal diagnosis of TGA, greater degree of hemodynamic instability and hypoxemia, underlying genetic abnormality, inadequate nutrition, complex TGA, prolonged bypass times, peri-operative complications (e.g., NEC), use of DHCA, and need for ECMO [86]. This highlights the importance of fastidious attention to neuroprotection in the perioperative period, with optimal timing of surgery, anesthetic and surgical techniques, and monitoring to improve neurodevelopmental outcomes and quality of life in ASO neonates.

Outcomes for Rastelli

Overall survival after Rastelli operation has improved drastically in the last few decades from 52 to 93% at 20 years [87, 88]. Despite this, the re-intervention rate remains high, with approximately 40% of patients requiring re-intervention for RVOTO at 20 years [88]. The conduits do not grow with the child, become stenosed overtime, and are at a risk of calcification; therefore, serial conduit replacements are inevitable. However, extension of the VSD at the time of operation has nearly eliminated the need for reintervention for LVOTO. Atrial and ventricular arrythmias occur commonly and sudden death from arrythmia is a problematic long-term complication. Although RV and LV failure may also occur, the Rastelli operation protects the RV from chronic regurgitation, unlike the REV and Nikaidoh procedures.

Outcomes for Senning and Mustard procedures

Mustard and Senning procedures have low operative mortality, and overall survival for all patients is approximately 75% after 25 years [73]. Long-term sequelae, however, are common and are largely related to RV failure, arrythmias, and baffle complications. Mustard and Senning procedures were the original mainstay for surgical correction of TGA, but as a result of the morphological RV remaining as the systemic ventricle, they have been largely superseded by the ASO. All adults develop some degree of RV dysfunction, with 10% of adults requiring hospital admission for CHF after 20 years [73, 89]. Common baffle-associated complications include leak, stenosis, and/or intractable atrial arrhythmias [90]. Scarring around the sinus node and intra-atrial baffle sutures results in sick sinus syndrome and atrial flutter, respectively. Sudden, presumed arrhythmogenic death and myocardial failure are the most frequent causes of late death in these patients [91].

KEY POINTS: SURGICAL OPTIONS

- The most common procedure for d-TGA is the ASO; others include the Rastelli procedure and (rarely) the atrial switch.
- Left ventricular mass involutes in d-TGA/IVS as PVR decreases postnatally.
- ASO repair is usually performed in the first 2–3 weeks of life.
- Long-term complications include PA stenosis, coronary artery insufficiency, early atherosclerotic disease, neoaortic regurgitation, and neurodevelopmental impairment.

Anesthetic considerations and perioperative management

It is essential for the anesthesiologist to have a detailed understanding of the pathophysiology of the TGA lesion, other associated anomalies, the overall condition of the child, and any interventions that have been undertaken to stabilize the child.

Preoperative assessment

A thorough and detailed anesthetic pre-op assessment is focused on issues relevant to any neonatal high-risk surgery and pertinent to TGA physiology. Pre-operative optimization and assessment is a multidisciplinary endeavor with the involvement of expert surgeons, cardiologists, anesthetists, and intensivists. Cardiac multidisciplinary conferences to tailor peri-operative care to the patient and discuss surgical planning, surgical timing, pre-operative optimization strategy, and clinical course are best practice.

The pre-operative assessment should focus on:

- Adequacy of intercirculatory mixing
  - PGE/BAS/ASD/number of communications and direction of shunts
- Associated cardiac conditions
  - IAA/Coarctation/VSD/LVOT
- Associated co-morbidities – Congenital/acquired (e.g., NEC/IVH) – does surgery need to be delayed?
- Age of Child
  - >1 month in TGA/IVS – LV mass involutes, may need alternative surgical strategy (PA banding) or back up EMCO
  - >2 months TGA VSD – pulmonary over-circulation leading to PAH

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- Details of TGA type and cardiac anatomy
  - Size of VSD, ventricular function, coronary anatomy, pulmonary valve structure, and function
- Elevated PVR
  - Patients with high PVR may present with inadequate mixing and require urgent surgery with a suboptimal acid–base balance
- Clinical examination – Pre/post ductal saturations, Reverse differential cyanosis
- Cardiorespiratory status and current support
  - Arrhythmias, pulmonary over-circulation, CHF
  - Inotropes, mechanical support, iNO, ventilatory support (high flow nasal cannula, CPAP, mechanical ventilation)
- Pre-operative blood tests – complete blood count/electrolytes/coagulation panel and cross match
- Family rapport, detailed informed consent, and discussion of perioperative course
- Team brief – surgeons/perfusion/scrub/anesthetic team on day of operation to discuss concerns, surgical approach, and perfusion strategy.

Anesthetic goals

Anesthetic goals include:

- Maintain ductal patency in duct-dependent lesions
- Maintenance of stable cardiovascular parameters
  - Maintain HR, sinus rhythm, pre-load, and myocardial contractility to maintain cardiac output (CO) – reduced CO reduces mixed venous oxygen saturation (SVO_2) and therefore decreases arterial saturation
- Avoid increase in PVR relative to SVR
  - An increase in PVR will reduce pulmonary blood flow and hence reduce intercirculatory mixing.
  - In PAH or mild/mod LVOT, ventilatory strategies can be used to reduce PVR, increase pulmonary blood flow, and increase mixing
- Avoid reduction in SVR relative to PVR
  - Decreased SVR increases recirculation of systemic venous blood and decreases arterial saturation

Anesthetic intraoperative management

On arrival in the anesthetic room after pre-op checks are complete and consent form is checked, monitoring is placed – SpO_2 (pre- and post-ductal), ECG, and NIBP. Induction can be intravenous or inhalational and should be tailored to the child. Our institution would use a combination of an opiate, an inhalational agent, and a muscle relaxant. A high-dose opioid technique has many advantages including attenuating the stress response, decreasing post-op morbidity, reducing coagulopathy and transfusion requirements [92, 93]. Fentanyl is the most commonly used opioid for induction in the United Kingdom, with doses ranging from 30–300 ug/kg, usually 10 mcg/kg is required as a minimum prior to incision. It is important to note that inhalational induction may be prolonged in patients with TGA due to high pulmonary re-circulation; it is therefore important to avoid high percentage sevoflurane for induction as myocardial depression may occur rapidly. Pancuronium, if available, at the dose of 0.1 mg/kg can be used for muscle relaxation, which is advantageous due to its long half-life. Pancuronium has vagolytic and sympathomimetic effects, thus inducing tachycardia, which can be blunted with co-administration of fentanyl. A nasal endotracheal tube in inserted, if possible, to aid comfort in the post-operative period.

Once intubated, arterial and central venous access is obtained. Radial arterial access is the preferred location due to the increased incidence of arterial thrombosis in femoral arterial lines, particularly in patients with cyanotic heart disease [94]. A central venous line is also inserted; preferably an internal jugular CVC, but if SVC cannulation is required for VSD closure a femoral central line may be preferable. Central venous pressure measurement is then established.

Once transferred into the operating theatre, core and peripheral temperature probes are placed, and NIRS is applied to the forehead. A urinary catheter is inserted to monitor urine output intraoperatively and throughout the postoperative course. The patient is then positioned appropriately; all lines are checked, secured, and padded prior to draping. A transesophageal echocardiography probe (TEE) is inserted after sufficient fentanyl has been administered to blunt cardiovascular response to the stimulating effect of its insertion. If a neonatal probe is available, then children weighing as little as 2.5 kg are suitable for this transesophageal approach. Epicardial echocardiography is preferred in some centers and is used in children with failed transesophageal placement or if they weigh less than 2.5 kg. The benefit of immediate echocardiography after separating from bypass is indisputable, particularly for the assessment of myocardial function, detection of residual defects, assessment of neo-aortic valve regurgitation, and adequacy of coronary anastomosis. Careful placement of the TEE probe is of paramount importance because of the higher risk of complications in neonates. TEE risks include compression of structures adjacent to the esophagus, predominantly the trachea and LA, leading to ventilatory or hemodynamic compromise respectively. The most frequently occurring risks involve esophageal or oropharyngeal trauma leading to dysphagia or hoarseness post-operatively, with most serious complication of esophageal perforation being extremely rare. A pre-bypass TEE examiniation is often preformed to clarify cardiac anatomy.

KEY POINTS: ANESTHETIC GOALS

- Maintain the PDA with PGE_1 in the duct-dependent circulation.
- Avoid increases in PVR and reductions in SVR to ensure adequate pulmonary blood flow and avoidance of recirculation of pulmonary venous blood.
- Maintain HR, sinus rhythm, pre-load, and myocardial contractility to maintain cardiac output (CO).

Pre-bypass Management

Due to the effects of anesthesia on the parallel systemic and pulmonary circulations, the pre-bypass period requires close attention from the anesthesiologist. PVR should be carefully optimized as an increase in PVR will decrease pulmonary blood flow and reduce intercirculatory mixing. SpO_2 is influenced by

the ratio of PVR to SVR. Arterial saturations usually sit around 75%; further desaturation in this period may relate to issues with ventilation (secretions, endobronchial intubation etc.) or decreased cardiac output. A reduction in cardiac output decreases systemic venous saturation and hence arterial saturation, which can be improved with the administration of a fluid bolus or inotropes. A decrease in SVR results in recirculation of venous blood and decreased arterial saturation, boluses of vasopressors (phenylephrine is used in our institution) can be used to counteract this decrease. If these interventions do not result in an improvement in arterial saturation, FiO_2 can be increased as a short period of high oxygen administration is unlikely to result in acute cardiogenic shock from pulmonary over-circulation.

Bypass

Cannulation for CPB is usually achieved following systemic heparinization using bicaval cannulation in the superior and inferior vena cava, avoiding the need for deep hypothermic circulatory arrest (DHCA). Single venous cannulation of the RA can be used but this requires a brief period of DHCA to repair the septal defects or aortic arch. The ASO is performed prior to the closure of any intracardiac defects as these will act as cardiac vents. The pump is primed with packed red cells and fresh frozen plasma (FFP) and during bypass hematocrit is maintained at ~30% [95]. An adequate mean arterial pressure is essential for ensuring adequate cerebral NIRS. A pH stat technique is preferred for acid-base management as it has been shown to increase cerebral NIRS, suggesting greater cerebral oxygenation during CPB in cyanotic patients with heart disease [96].

Antibiotics

Prophylactic antibiotics are administered 30 minutes prior to skin incision. Specific antibiotics administered are based on local policies and post-natal age.

Attenuating the systemic inflammatory response syndrome

The proinflammatory state as a consequence of cardiac bypass has been postulated to have deleterious consequences to cardiac function, such as low cardiac output syndrome (LCOS) and increased need for pharmacological or mechanical support leading to increased post-operative morbidity and mortality [97]. Corticosteroids are used by many centers to attenuate this inflammatory response while providing myocardial protection, but their use remains controversial, with no large-scale randomized controlled trials (RCTs) to provide clarity. Multiple trials have suggested that corticosteroids provide no significant benefit to justify their use, with some evidence that there is increased morbidity in lower risk groups due to increased risk of infection and prolonged length of stay [97–99]. A recent meta-analysis demonstrated attenuation of the cardiac bypass-induced inflammatory response, greater preservation of renal function, and lower mortality with steroid administration. However, the numbers are limited, and a larger prospective randomized study is still needed to verify the use of prophylactic steroids in pediatric cardiac patients [100]. A recent RCT in adults showed methylprednisolone had no significant effect on mortality or major morbidity after cardiac surgery [101]. Steroids are not routinely used in our center as a means of reducing the proinflammatory state of surgery and CPB. Systemic inflammatory reaction after bypass can also be reduced by a high dose fentanyl technique, heparin-coated bypass circuits, adequate heparinization, and the utilization of modified ultrafiltration (MUF) after bypass [93, 102, 103]. See Chapter 12 for further discussion of the inflammatory response.

Near infrared spectroscopy and neuromonitoring

Minimizing neurological morbidity associated with congenital cardiac surgery has become increasingly important as mortality has fallen dramatically with improvements in pre-natal diagnosis, intensive care treatment, and surgical technique [104]. Brain injury in these patients is a multifactorial process with risk factors from the pre, intra and post-operative period. Mechanisms of pre-operative brain injury include hypoxemia, prolonged time to surgery, and cardiac arrest [105] (Table 29.4). McQuillen et al. reported that balloon atrial septostomy is associated with pre-operative stroke in neonates with TGA although this is controversial, with recent data indicating that there was no association between brain injury and BAS [40, 41]. The Boston group highlighted that CPB is a clear risk factor for intra-operative neurological complications, likely due to hypoxia or ischemia from disturbances in cerebral perfusion [106–108]. This is particularly significant during periods of low flow CPB and deep hypothermic cardiac arrest. Near-infrared spectroscopy (NIRS) is a noninvasive, continuous monitoring of cerebral oxygenation that is not observable from standard monitoring technology [109]. It measures regional oxyhemoglobin saturation (rSO_2), through concentrations of oxyhemoglobin and deoxyhemoglobin, which correlates closely with jugular venous saturations in children [110, 111]. Several studies have demonstrated the benefit of NIRS during CPB and its accuracy in correlating with vital parameters [112]; however, there is limited knowledge on how to manage CPB according to cerebral oximetry values. Although there is some data that intervening to improve low intra-operative NIRS values may decrease the incidence of post-operative neurological adverse outcomes, [113] a randomized control trial is required. Our institution continues to record

Table 29.4 Risk factors for neonatal brain injury in patients with TGA

Preoperative	Intraoperative	Postoperative
Post-natal diagnosis of TGA	Hematocrit <25%	Low arterial PaO_2
Length of time to surgery	Decreased NIRS	Low BP
Low arterial hemoglobin saturation	Prolonged circulatory rrest	NIRS <45% for >3 hours
Cardiac arrest	CBP strategy	Morphologically immature brain
Morphologically immature brain		
Balloon atrial septostomy		

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NIRS trends in the intensive care unit during the initial postoperative period due to on-going risk of brain injury secondary to hypotension and hypoxemia [114]. See Chapter 14 for further discussion of neurological monitoring and outcomes.

Anticoagulation and thromboelastography/thromboelastometry

Management of anticoagulation during CPB is of fundamental importance due to the creation of a procoagulant state resulting in both hemorrhagic and thrombotic complications. Infants with cyanotic heart disease are at a particular risk and experience higher surgical morbidity and mortality compared to older children [115]. This is due to the immaturity of the coagulation system leading to a deficiency of antithrombin, hemodilution of clotting factors, and physiological changes associated with cyanosis [116, 117]. To minimize the risk of thrombosis heparin is administered while on CPB at an initial dose of 300–400 units/kg, ensuring that activated clotting time (ACT) is >350 seconds (or over three times baseline) and maintained throughout bypass. Children require higher doses of heparin than adults due to their ability to metabolize heparin more rapidly as well as their lower levels of antithrombin [118]. Due to relative heparin resistance in these infants, there may be ineffective suppression of thrombin generation [119]. This increases the likelihood of clot formation in the post-bypass period or microthrombi formation during bypass, causing the depletion of clotting factors resulting in a more severe coagulopathy post-bypass. Excessive anticoagulation, on the other hand, may place patients at risk of postoperative bleeding complications, even after its neutralization [120]. ACT is used to monitor the anticoagulant effect of heparin during bypass. It is a measure of whole blood coagulation, but its accuracy is limited by multiple factors that prolong ACT commonly encountered during CPB (hemodilution, hypothermia and impaired platelet function) even when the heparin dose is inadequate.

ACT correlating poorly with heparin effects has led to the use of patient-specific heparin management [121]. Patient-specific heparin management systems use a heparin dose-response test to determine the individualized response to heparin, along with heparin level monitoring. This has been more effective at suppression of thrombin than conventional heparin dosing and measurement, resulting in reduced blood loss and need for transfusion [122, 123].

Protamine sulfate is used to neutralize heparin at the end of bypass, by binding ionically to unfractionated heparin causing dissociation from the heparin–antithrombin complex. Dosing protamine can be problematic; accurate dosing requires knowledge of the circulating heparin concentration. Insufficient neutralization of heparin will increase the risk of postoperative bleeding, while excessive protamine dosing causes a paradoxical anticoagulant effect [124]. This is further complicated by ultrafiltration, as heparin molecules are too large to pass through the filter, leading to increased heparin concentrations [125]. Protamine administration can be associated with adverse effects including catastrophic pulmonary hypertension and histamine related vasodilation; therefore, careful administration is required [126].

Bivalirudin, a direct thrombin inhibitor, is an uncommonly used alternative in maintaining anticoagulation during CPB. Bivalirudin does not require the presence of anti-thrombin to be effective; thus, it can be used successfully in patients with heparin resistance due to antithrombin deficiency, and it has the potential to provide more consistent anticoagulation in neonates [127]. Bivalirudin is also used in patients with heparin-induced thrombocytopenia (HIT) as well as anticoagulation for ECMO or ventricular assist devices [127]. Bivalirudin has multiple drawbacks to its use including no point-of-care test to monitor anticoagulation effect, with limited pediatric studies, and despite its removal from the circulation via ultrafiltration, the lack of a reversal agent raises the concern of increased postoperative blood loss [128].

Hyperfibrinolysis is activated during bypass, and it is one of the major contributing factors leading to post-bypass bleeding [129]. Prophylactic administration of antifibrinolytics including tranexamic acid (TXA), aminocaproic acid (EACA), and aprotinin have been shown to decrease postoperative bleeding and transfusion requirements after pediatric cardiac surgery [130, 131]. Debate exists around the optimal dosing and administration of tranexamic acid, although studies suggest that sustained antifibrinolysis (dosing pre, during, and post-bypass) provides the greatest reduction in blood loss [132]. Although further studies are required to clarify optimum dosing of tranexamic acid, current expert opinion suggests a loading dose of 30 mg/kg followed by a continuous infusion of 10 mg/kg/hour in children <1 year of age [133].

Aprotinin is a serine protease inhibitor that has been shown to decrease bleeding and shorten ICU stays in adults; however, its use is controversial. It was withdrawn from the U.S. market in 2008 due to reports of increased risk of renal failure and mortality in adults undergoing cardiac surgery [134]. To date, there is no data to support similar findings in children. The use of aprotinin in neonates and children remains very controversial due to a lack of well-designed studies and an undefined safety profile; it is prudent to use lysine analogues (TXA and EACA) preferentially.

Thromboelastography and thromboelastometry

Conventional measures of coagulation such as PT, APTT, and ACT reflect the initial phases of coagulation but do not accurately predict post-op bleeding in neonates. Thromboelastography (TEG®) measures whole-blood coagulation profile incorporating interactions between platelets, fibrin polymerization, and fibrinolysis. TEG is therefore considered a better predictor of postoperative bleeding than conventional laboratory measurements, and its use has been found to significantly reduce postoperative bleeding, RBC transfusion, and length of ICU stay [135]. It is important to note TEG use may lead to excessive use of platelets and fibrinogen; therefore, abnormal TEG should be corrected in only the bleeding patient [136]. Its rapid generation of information is advantageous when targeting blood product administration after bypass [137]. Thromboelastometry (ROTEM®) has many similarities with TEG®, and both can assist in diagnosing the cause and aiding decision-making in the treatment of coagulopathy. Chapters 11 and 16 present further discussion of coagulation monitoring during and after bypass.

Separation from bypass

Separation from bypass requires clear communication between the surgeons, anesthesiologists, and perfusionists to ensure the transition occurs smoothly. The child must be adequately re-warmed, ventilation re-established, and the heart de-aired, with good ventricular function and no evidence of arrythmias or ischemia. Inotropes will be required to support the myocardium after bypass and need to be established prior to separation. Our institution favors epinephrine (although dopamine and dobutamine can also be used) with milrinone for its valuable inodilator properties. Milrinone is particularly important in reducing the LV afterload, as the LV will now be required to support the systemic circulation. Poor LV performance is of particular concern in patients undergoing late repair of TGA.

Preceding separation, pacing wires are placed and close inspection of the coronary arteries is required to ensure sufficient coronary patency (and perfusion) with minimal bleeding from the surgical anastomosis and suture lines. Inadequate invasive pressures and ST segment abnormalities can indicate coronary artery occlusion or kinking and require prompt rapid assessment of coronary patency. This may be difficult to visualize with TEE; hence, epicardial echography can be used, or surrogate markers of coronary patency such as regional wall motion abnormalities or mitral regurgitation may be observed. Coronary post-CPB myocardial dysfunction may be due to air in the coronaries, inadequate coronary transfer, poor myocardial protection, or a deconditioned LV. Prolonged ischemia must be avoided, and CPB may need to be resumed to fully assess the coronary arteries and any other precipitating factors to prevent end-organ hypoperfusion. Separation from bypass is often facilitated with low LAP (e.g. 2–5 mmHg) and a gradual reduction in pump flow.

On separation from bypass, blood volume may be required, which can be given by the perfusionist via the aortic cannula. Inotropes should be titrated to optimize cardiac output and organ perfusion whilst ensuring afterload is reduced. Once cardiovascular stability has been achieved, a period of modified ultrafiltration (MUF) can begin. MUF removes inflammatory mediators, which are thought to cause myocardial depression, from the circulation; although the most beneficial mechanism is due to the increase in hematocrit and concentration of clotting factors and pressor agents, which has been shown to significantly decrease bleeding in children after cardiac surgery. All children will require blood and clotting products once bypass has been terminated and protamine administered. Platelets, cryoprepitate, and FFP are available and given in incremental 5–10 mL/kg aliquots to prevent overdistension of the heart. Overdistention can lead to stretching of the newly implanted coronary arteries and subsequent myocardial ischemia. A left atrial pressure (LAP) line is placed prior to separation from bypass, providing valuable information immediately post bypass and can remain in situ in the post-op period to monitor LV dysfunction. A high LAP is a marker of excessive LV preload, which is not well tolerated by the non-compliant LV. Raised LAP also results in PA distension, which may compress the newly implanted coronary arteries, as the PA now sits anterior to the aorta. Fluid must be given cautiously, targeting LAPs of between 8–10 mmHg, with mean arterial pressures of 35–45 mmHg being sufficient to maintain adequate tissue perfusion. In the acute setting, if LAP is excessively high, a small volume of blood can be withdrawn from the central line to avoid precipitating fulminant LV failure.

Pulmonary vascular resistance can be increased due to preoperative exposure to increased pulmonary flow leading to reactive pulmonary vasculature. Inhaled NO should be readily available and instituted with a low threshold. If RV pressures are over two-thirds systemic while on iNO, direct measurement of RV and PA pressures is required to evaluate for potential obstruction across the neo-pulmonary anastomosis.

Chest closure should occur at the end of the operation providing there is hemodynamic stability and minimal bleeding. Rarely ECMO is required for temporary hemodynamic support. In this case, the chest is splinted open with a stent, and the wound covered with a Silastic™ dressing. The goal is to close the chest in the cardiac intensive care unit in the next 24–48 hours once stabilized.

Advances in perioperative care have enabled a drive toward early extubation after surgery for congenital heart disease. Prolonged intubation increases the risk of associated laryngeal trauma, pneumonia, and atelectasis, as well as increasing the unfavorable hemodynamic consequences on right heart function. There is some preliminary data to suggest "fast-track" extubation (within 6 hours) is safe, increases parental satisfaction, and results in reduced length of hospital stay – without an increase in morbidity and mortality [138, 139]. Evidence is limited and large multicenter trials are required to determine whether early extubation should become the standard of care. Patients with high oxygen requirements, ventricular dysfunction, and prolonged bypass times would not be suitable candidates for early extubation. Our institution uses a high dose opioid technique which reduces morbidity and mortality by suppressing the stress response to surgery but prevents early extubation [93].

KEY POINTS: ANESTHETIC MANAGEMENT

- Induction can be inhalational or intravenous.
- Maintenance with balanced opioid/inhalational technique is often preferred for better hemodynamic control.
- Invasive monitoring (arterial line, central venous pressure) is placed after nasotracheal intubation.
- Nasopharyngeal, rectal, and skin temperatures, neuromonitoring, and TEE or epicardial echocardiography probes are employed.
- Antibiotic prophylaxis is administered 30 minutes before skin incision.
- Heparin is administered with an ACT goal of >350 seconds; heparin level measurement systems are often very useful.
- CPB weaning is accomplished after rewarming, intracardiac air is removed, and cardiac function is acceptable, with acceptable rhythm and no signs of ischemia.
- Echocardiography is performed before sternal closure.

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Postoperative management of the arterial switch operation

Postoperatively, patient management takes place on the intensive care unit and is tailored to preoperative condition and the surgery performed. Patients are transferred to intensive care intubated, where sedation is continued. Our priority is to achieve hemodynamic stability and carry out careful observation for potential complications.

Common immediate post-op complications

Bleeding

Bleeding is a common complication in the early post-op period after the ASO, with early post-op hemorrhage an independent risk factor for increased morbidity and mortality after cardiac surgery [120, 140]. Multiple suture lines across great vessels after an ASO increases the risk of surgical bleeding, exacerbating coagulopathy, and hence medical bleeding. Coagulopathy necessitating administration of large volume of blood products (platelets, cryoprecipitate and FFP) can deleteriously affect pulmonary and myocardial function (via overdistention and stretching of the newly implanted coronary arteries). Bleeding is closely monitored in the post-op period with chest drain losses of >4 mL/kg/hour being indicative of significant bleeding. Avoidance of arterial or pulmonary hypertension is also imperative to minimize surgical bleeding from the numerous suture lines.

Left ventricular function and low cardiac output syndrome

Cardiovascular parameters and clinical findings must be closely observed in the intensive care unit post-operatively, with management directed toward ensuring adequate tissue perfusion (Table 29.5). Monitoring is continued from the intra-operative period with particular attention paid to LAP, lactate, SvO_2, and NIRS. MAPs of 40–45 mmHg are usually sufficient in these patients, with filling targeted to a LAP ideally between 5–8 mmHg, with no advantage to tissue perfusion with LAP above 10 mmHg. This is because ventricular diastolic function is poor after the ASO, and volume overload is not tolerated. Overfilling post ASO may lead to cyclical situation, where an already struggling LV dilates and distends (particularly in the context of mitral insufficiency) resulting in stretching or kinking of the coronary arteries, further worsening the myocardial insult and triggering further LV dilatation. Raised LAP can exacerbate this problem, raising PAP that can compress the coronary ostia due to its new anterior position after the LeCompte maneuver. Fluid administration must therefore be cautious, and boluses should be given in aliquots of 5 mL/kg with impact closely monitored. If required, blood can be withdrawn from the arterial or central line to reduce LAP pressure.

Table 29.5 Intensive care unit targets post arterial switch operation

Parameter	Target
MAP	>45 mmHg
LAP	5–8 mmHg
SvO_2	>60%
Lactate	<3 mmol/L
Urine output	>0.5 mL/kg/hour

Box 29.2: Causes of low cardiac output after the arterial switch operation

- Coronary artery insufficiency
- Low cardiac output syndrome
- Untrained LV
- Unprotected myocardium after cardiopulmonary bypass

Myocardial function after an ASO may be impaired for multiple reasons related to coronary insufficiency, inadequately trained left ventricular mass and insufficient intra-operative myocardial protection during bypass (Box 29.2). Low cardiac output after an ASO must always raise the suspicion of coronary insufficiency first. If coronary artery insufficiency is suspected, prompt surgical review with possible intervention and revision is required. Low cardiac output will also be the clinical presentation in patients with primary myocardial dysfunction, most commonly occurring in patients with borderline pre-op LV function or inadequate LV mass. Inotropic support is therefore required while the LV adapts to support the systematic circulation. Nonspecific low cardiac output could be due to LCOS (Low cardiac output syndrome) – a serious yet commonly occurring complication of bypass, with 25% of children with CHD affected after cardiac surgery. LCOS results in insufficient cardiac output to meet systemic oxygen demand, usually occurring 6–18 hours after cross clamp removal. The etiology of LCOS is multifactorial and appears to be related to the inflammatory response to CPB, myocardial reperfusion injury, and ischemia from aortic cross clamping [141]. LCOS contributes to increased morbidity and mortality; therefore, it should be anticipated, with early identification and aggressive treatment of paramount importance. The clinical parameters indicating LCOS (persistently low MAP), poor peripheral perfusion, increasing lactate, and raised LAP), may also be caused by myocardial insufficiency and hence requires urgent investigation with echo.

Arrythmias

Neonates undergoing an ASO will be predisposed to arrythmias in the early post-op period; this is associated with increased mortality after cardiac surgery; therefore, early recognition and management is of paramount importance [142]. The most commonly occurring arrythmias include supraventricular tachycardia (SVT), junctional ectopic tachcardia (JET), or ventricular tachycardia (VT) and may relate to multiple factors: line placement, electrolyte imbalance, inadequate myocardial protection after bypass, LCOS or due to surgical trauma, or inflammation [142]. Arrythmias, especially VT, are frequently indicative of coronary insufficiency, which is more likely with unusual coronary anatomy (single coronary artery, intramural coronary arteries) due to the technically demanding nature of the coronary transfer.

Pulmonary hypertension

Pulmonary hypertension or pulmonary hypertensive crisis may complicate the post-op course, particularly in patients with TGA/IVS; it typically occurs within the first 48 hours

post-op and usually coincides with a decrease in cardiac index [141]. Although the exact mechanism is unknown, it is likely related to ischemia-reperfusion injury post bypass or acute ischemia leading to left ventricular dysfunction, with backward transmission of elevated left ventricular filling pressures to the pulmonary circulation. Patients with D-TGA are prone to increased pulmonary vascular reactivity due to pulmonary over-circulation contributing to the degree of PH. Inhaled NO, increased depth of sedation, hyperventilation, and paralysis are used as treatment strategies to help reduce pulmonary bed reactivity. An echo should be performed to assess the degree of pulmonary hypertension and biventricular dysfunction as well as looking for residual shunts or branch pulmonary stenosis following LeCompte maneuver.

Respiratory support and drains

After return from the operating room the child remains sedated and mechanically ventilated, using lung protective ventilation strategies to avoid barotrauma. Respiratory support is gradually weaned over the first 12–24 hours. Patients will need to remain ventilated beyond this if they are hemodynamically unstable, develop arrythmias or continue to bleed. Patients who return to CICU with an open chest will need to stay ventilated until 24 hours after chest closure, providing they remain stable. Although there is a push in some centers toward early extubation, our center will wait until relative stability has been achieved. This includes:

- Hemodynamic stability – an adequate blood pressure, heart rate and LAP with low inotropic support
- Minimal ventilatory requirements
- A negative fluid balance – a good urine output is usually a positive indicator and is essential to remove excessive fluid from the myocardium, lungs, and other organs
- Chest radiograph without significant lung pathology
- Normalized blood gases
- No signs of sepsis.

Mediastinal drains are closely monitored in the early post-operative period as they are a visible indicator of post-op bleeding. In the first four hours bleeding between 0–4 mL/kg/hour is normal, with chest drain output usually decreasing in the ensuing hours. Bleeding above 4 mL/kg/hour may signify surgical bleeding or uncorrected coagulopathy, requiring directed blood product administration and urgent surgical review. A sudden reduction in previously brisk bleeding associated with hemodynamic instability may indicate cardiac tamponade necessitating urgent action. Chest drains stay in situ until there is minimal drainage, typically around day 3 post-operatively. After chest drain removal, a chest radiograph will be performed to rule out pneumothorax, atelectasis or residual pleural effusions.

Sedation and analgesia

An individualized plan optimizes patient comfort and helps to reduce the stress response whilst minimizing hemodynamic compromise. While insufficient sedation may cause ventilation desynchrony (with deleterious effects on gas exchange) and risks inadvertent removal of tubes, drains or lines; excessive sedation prolongs ICU stay, delays recovery and increases the symptoms of withdrawal. Sedation assessment scores (e.g. COMFORT score) should be measured at regular intervals to ensure sedation and analgesia are optimized and titrated to individual patient need. If possible, high dose and protracted use of sedation should be avoided to minimize the effects of physical dependence and withdrawal. For this reason, short acting drugs are preferred, reviewed regularly and weaned as soon as appropriate.

Our institution commonly uses a combination of opioids (morphine or fentanyl) and alpha agonists (dexmedetomidine or clonidine) delivered via continuous infusion. Occasionally benzodiazepines such as midazolam are used. Dexmedetomidine is particularly useful in this patient cohort due to limited effects on respiratory function, facilitating early or "fast-track" extubation while reducing the need for additional sedation or analgesic agents [45, 143, 144]. Dexmedetomidine has significant cardiovascular benefits as it has been found to be effective in reducing post-operative arrhythmias including SVT, JET, and VT and reduces vasopressor agent dosing for children with catecholamine- refractory cardiogenic shock [145–147]. Although dexmedetomidine has been shown to cause a dose related decrease in heart rate, it has not been found to be clinically significant in infants after congenital heart surgery [148]. Neuromuscular blockade post-operatively may be required in management of JET, LCOS, or a pulmonary hypertensive crisis, although their use should be avoided where possible. Use of neuromuscular blocking agents in critically ill children is associated with increased mortality and high rates of physical and cognitive disability [148].

Renal support

Transient acute kidney injury is common after cardiac surgery and CPB leading to increased morbidity and mortality [149]. Approximately 50% of neonates undergoing ASO have some degree of renal injury, with 10% requiring renal replacement therapy (RRT). Renal failure is multifactorial, predicting which patients will develop acute kidney injury (AKI) or require RRT remains difficult. Furosemide is started 8–12 hours after return from theatre. In our institution, all neonates have a peritoneal dialysis (PD) catheter inserted at the time of surgery. Prophylactic insertion of a PD catheter has shown diminished timescales for achieving negative fluid balance, reduced time to extubation, and lessened ionotropic requirement [150].

Fluids and electrolytes

Due to the risk of volume overload resulting in raised LAP and worsening LV dysfunction, fluid must be given cautiously post-operatively. Fluid boluses should be avoided if possible; if required for volume resuscitation due to bleeding, blood products should be given in 5–10 mL/kg aliquots, paying close attention to the LAP. Maintenance fluid should be administered at 30–50% total fluid requirements in first 24 hours post-op and should not exceed 50–75% until extubation. Electrolytes should be carefully monitored and corrected to ensure Mg++ >1 mmol/L, K+ 4–5 mmol/L and Ca++ >1.2 mmol/L.

Feeding and nutrition

Nasogastric feeds should be started as soon as hemodynamic stability has been achieved. Early feeding can prevent gastric translocation, minimize the loss of lean body mass, and support vital organ function [151]. If enteral feeding is not started within the first 24 hours, parental nutrition should commence. Once extubated, infants with stable respiratory parameters can be fed orally.

Sepsis

Prophylactic antibiotics are started at induction (30 minutes prior to incision) and continued for 24 hours post-operatively, as per local guidance. Patients with an open chest continue on broad spectrum antibiotics until the chest is closed. Targeted measures and clinical bundles should be followed to minimize the risk of post-operative infections such as ventilator-associated pneumonias, line infections, and sternal wound infections.

Congenitally corrected TGA (L-TGA)

Incidence

Congenitally corrected transposition of the great arteries (ccTGA) is an uncommon cardiac defect, accounting for less than 0.5% of all congenital heart disease.

Anatomy

Congenitally corrected transposition of the great arteries (ccTGA), or levo-TGA (L-TGA) is a rare disease characterized by both atrioventricular and ventriculoarterial discordance. ccTGA is also commonly referred to as double discordance or ventricular inversion (due to reversal of ventricular positioning) Consequently, a right-sided RA connects via the mitral valve to a morphological LV to a right-sided PA. The left-sided LA drains via the tricuspid valve into a morphological RV to supply a left-sided aorta (Figures 29.18 and 29.19). ccTGA may present as situs solitus (the morphological left ventricle is located on the right, with a left sided aorta) or situ invertus.

Situs invertus ccTGA is an extremely rare lesion, with this variant accounting for one-third of ccTGA cases/lesions. Situs invertus ccTGA results in an anatomic mirror image of L-TGA and despite anatomical differences, pathophysiology of the disease is the same [153].

During embryological development, looping of the heart is required to ensure correct anatomical arrangement of the four chambers. In ccTGA the primitive heart loops toward the left (levo-bulboventricular) rather than following the usual right-sided looping (dextro-bulboventricular), resulting in abnormal atrioventricular and ventriculoarterial connections. This double discordance results in a series circulation; deoxygenated venous blood returns to the heart and oxygenated pulmonary venous blood is transported to the systemic circulation. Although blood flow is physiological, problems arise due to the intrinsically abnormal tricuspid valve and progressive decline in RV function, as it is poorly adapted to supporting the systemic circulation. In addition to this, >90% of patients have associated cardiac abnormalities, with a broad spectrum of severity.

Associated anatomic features in addition to AV and VA discordance that complicate ccTGA include [154]:

- Perimembranous or malaligned VSD (50–80%)
- Multiple or remote VSDs
- Multilevel LVOTO (50–70%) secondary to pulmonary atresia and subpulmonary or pulmonary stenosis
- Tricupsid valve anomalies (25–90%)
- Straddling or overriding AV valves
- Abnormalities and disturbances of the AV conduction system
- Ventricular hypoplasia
- Coronary anomalies
- Dextrocardia with or without situs abnormalities.

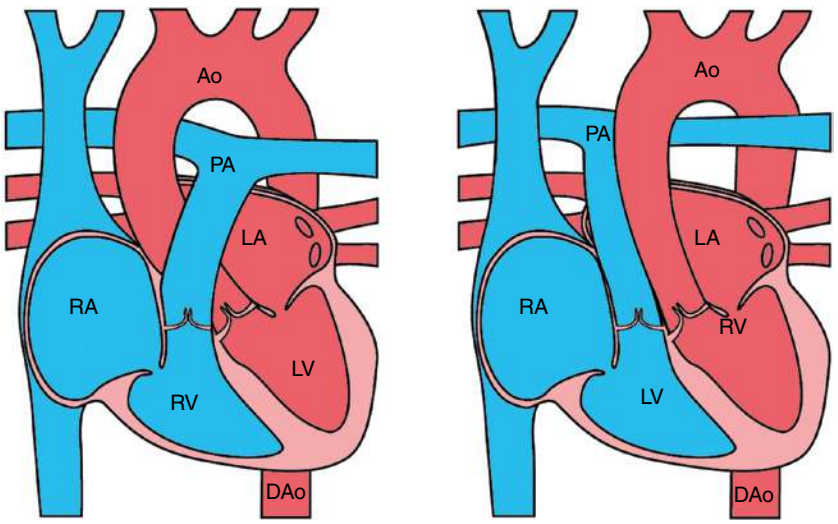


Figure 29.18 Congenitally corrected transposition of the great arteries (ccTGA). (A) Normal anatomy. (B) ccTGA – blood flow in corrected transposition. Ao, aorta; PA, pulmonary artery; LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle; DAo, descending aorta.

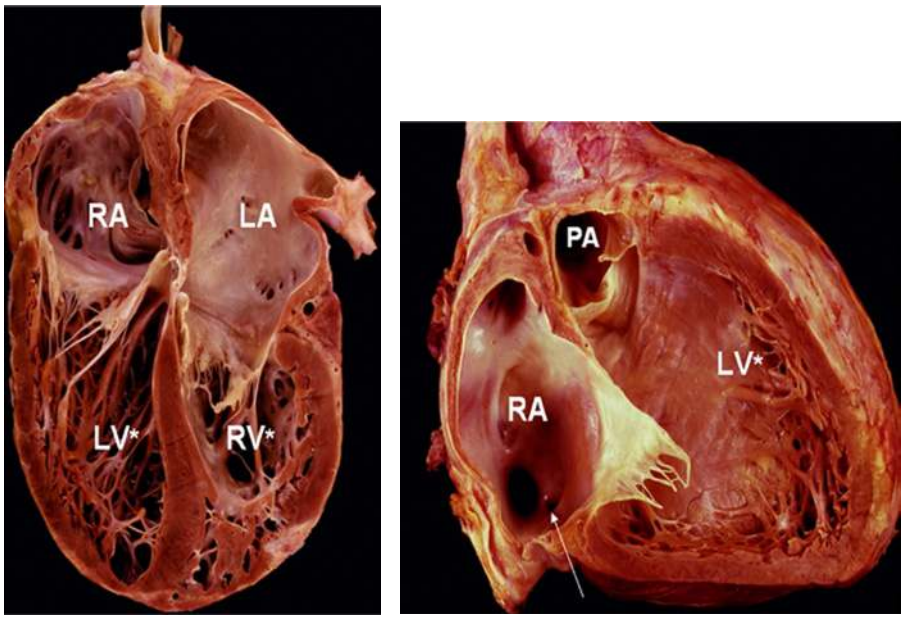


Figure 29.19 Anatomic section of heart from a patient with ccTGA. (A) Four-chamber view with the right AV valve located cephalad to the AV valve. (B) Long-axis view with the arrow pointing to the coronary sinus ostium. Note a relatively thin and indistinct Eustachian ridge separating the CS from the inferior vena cava. AV, atrioventricular; ccTGA, congenitally corrected transposition of the great arteries; CS, coronary sinus; LA, left atrium; LV, morphologic left ventricle; PA, pulmonary artery; RA, right atrium; RV, morphologic right ventricle. (Source: Bottega et al. [152]. Reproduced with permission of Elsevier.)

A VSD is present in approximately 70% of patients and is most commonly the result of malalignment between the atrial septum and the inlet of the ventricular septum, although defects can be found anywhere in the ventricular septum. LVOTO occurs in over 50% of patients and is nearly always associated with a VSD. Subpulmonary/valvular stenosis is the most frequently occurring manifestation of LVOTO and is usually due to posterior deviation of the conal septum or AV valve tissue. Isolated pulmonary valve stenosis is rare. Tricuspid valve abnormalities occur in >90% of patients, although this will result in functional consequences in approximately half of the patients [153]. The valve is described as "Ebstein-like." Posterior and septal leaflets are tethered to the posterior RV wall which tends to limit the long-term functional reliability of the tricuspid valve in the systemic circulation. In contrast to an Ebstein's anomaly, apical displacement of the valve leaflets with ensuing arterialization of the right ventricle is rare.

The AV node position is abnormal and is located between the orifice of the RA appendage and the mitral valve annulus, rather than at the apex of the triangle of Koch. Many patients also have dual AV nodes. As a consequence of the AV node abnormality, disturbances of the AV conduction system are common and thought to be secondary to fibrosis of the junction between the AV node and the AV conduction system [155]. Complete heart block is the most common resulting arrythmia, with a progressive incidence of 2% per year [68].

Coronary anatomy in ccTGA

The coronary artery anatomy in ccTGA is a mirror image of the normal anatomy. The artery originating from the right-sided sinus gives rise to the left anterior descending (LAD) and the circumflex artery, thus being considered the morphological left coronary artery. Originating from the left-sided sinus, following the left AV groove and supplying the right ventricle is the morphological right coronary artery.

KEY POINTS: ASSOCIATED ANOMALIES IN CCTGA

- Common anomalies associated with ccTGA can be summarized as follows:
  - Perimembranous or malaligned VSD (50–80%)
  - Tricuspid valve abnormalities (25–90%)
  - Multilevel LVOTO (50–70%)
  - Dextrocardia (25%) with/without situs inversus
  - Interruption or abnormally situated conduction pathway

Natural history

Isolated ccTGA is a variable lesion, and its natural history is dependent on three main factors: RV function, tricuspid valve function, and the development of arrythmias. The RV is intended to support the low-pressure pulmonary circulation and is poorly adapted at sustaining the systemic load. While patients without associated cardiac lesions are asymptomatic in early life, over the course of a normal lifespan, heart failure is a common long-term complication.

Twenty-five percent of patients with isolated ccTGA develop congestive heart failure (CHF) by the fourth decade, which increases to 67% in patients with associated cardiac lesions [156]. The risk factors of heart failure in ccTGA relate to advancing age, presence of associated cardiac abnormalities, tricuspid regurgitation, significant arrythmias, tricuspid valve surgery, pacemaker implantation and open-heart surgery [156, 157]. The long-term systemic workload of the RV leads to tricuspid regurgitation, resulting in RV volume overload, in turn accelerating ventricular dysfunction and failure [158]. It is also suspected that abnormal perfusion plays a major role in the development of progressive RV dysfunction, due to a single coronary artery supplying the systemic ventricle [159].

Pathophysiology

In ccTGA, the TGA is physiologically corrected, giving rise to a normal series circulation where deoxygenated blood is oxygenated in the lungs prior to entering the systemic circulation. The morphological LV is the pulmonary ventricle and empties deoxygenated blood into the PA; the LA receives oxygenated blood from the pulmonary veins, which enters the aorta via the morphological RV.

This creates a unique pathophysiological condition in which the morphological right ventricle (RV) sustains systemic circulation from birth. As the RV is not designed to withstand systemic pressures over the course of a normal lifespan it must undergo various adaptive mechanisms to support the systemic load, including eccentric hypertrophy, fibrosis, and dilatation of the RV [160]. Right ventricular dysfunction will eventually occur, with heart failure as a common long-term complication. Tricuspid regurgitation is strongly associated with RV dysfunction and CHF; its mechanism is thought to be multifactorial. Due to exposure of the RV to systemic pressure, the ventricular septum bows towards the LV, resulting in a spherical RV shape. This pulls the septal attachments of the TV away from the annulus, resulting in progressive tricuspid regurgitation and exacerbating the volume overload on the systemic and morphologic RV. In addition, the TV is frequently dysplastic (most commonly the Ebstein-type abnormality), with this group more likely to develop significant TR and ventricular dysfunction earlier in life [161]. Late RV dysfunction will be compounded by chronic microvascular ischemia and inadequate perfusion via the single coronary artery supplying the hypertrophied mass of the RV [161].

Clinical presentation and diagnostic features

The majority of patients with ccTGA are diagnosed postnatally. While ccGTA may be detected on prenatal fetal ultrasound, particularly in specialized centers, diagnosis remains challenging, especially when associated defects are not present [162].

Timing of post-natal presentation is dependent on the presence and nature of associated cardiac abnormalities. Isolated ccTGA is very unusual, only occurring in <10% of patients. These patients are initially asymptomatic but may present in adult life with symptoms of tricuspid (systemic) valve regurgitation, conduction disturbances, impaired systemic ventricular function, and CHF [163]. Complete heart block is the most common arrythmia with symptoms of chest pain, fatigue, dyspnea, and poor exercise tolerance. Tricuspid valve regurgitation and impaired systemic ventricular function will present with signs of heart failure, including fatigue, reduced exercise tolerance, dyspnea, and peripheral edema.

The majority of patients have concomitant cardiac abnormalities and will present with signs or symptoms associated with the pathophysiology of these lesions:

- **VSD** – may present with a systolic murmur or signs of heart failure.
- **LVOTO** – Cyanosis may be a presenting feature in patients who have a VSD and severe LVOTO due to decreased pulmonary blood flow and a large pulmonary-to-systemic ventricular shunt.
- **Tricuspid valve abnormality** – may present with signs of right heart failure or respiratory distress, cyanosis or a systolic murmur.

Diagnostic testing

ECG – Q waves present in the right precordial leads, but absent in the left precordial leads are characteristic of ccTGA due to inversed septal depolarization due to ventricular inversion i.e., from right to left. Patients may also present with complete heart block due to disturbances of the AV conduction system. Complete heart block may even be detected antenatally, raising clinical suspicion of ccTGA.

CXR – ccTGA with levocardia may result in prominence of the upper left border of the mediastinum. Presence of mesocardia or dextrocardia may raise clinical suspicion of ccTGA.

Echo – Echocardiography is a reliable method for diagnosis of ccTGA and the presence of associated anomalies. The four-chamber apical view will show the more trabeculated morphological RV on the left and the smoother walled morphological LV on the right.

Cardiac MRI – Cardiac MRI is commonly used to further evaluate these complex lesions and is able to provide detailed information about anatomy as well as quantitative assessment of function and flow. Cardiac catheterization is reserved for assessment of those patients who have pulmonary vascular occlusive disease and is frequently carried out in conjunction with cardiac MRI to give detailed information about PVR.

KEY POINTS: CCTGA

- ccTGA is a rare defect with AV and VA discordance.
- The TGA is physiologically corrected and has normal series circulation where blood is oxygenated in the lungs before entering the systemic circulation.
- The morphological RV is the systemic ventricle.
- There is a high incidence of associated cardiac anomalies, in up to 98% of patients.
- Age at presentation and natural history depend on the combination and severity of associated defects.
- Surgical repair is either physiologic or anatomic.

Surgical options

Surgical treatment options have been available for over 50 years, but optimal surgical management of ccTGA remains controversial. Surgical strategies are divided into "physiological repair" (the morphological RV remains as the systemic ventricle) or "anatomic repair" (creating atrioventricular concordance with the LV and mitral valve acting as the systemic ventricle and AV valve.) The first surgical repairs for ccTGA were "physiologic" and performed by Anderson and Lillehei in 1957. In the past two decades, anatomic repair has been considered a better option despite its more complex nature due to the unfavorable long-term outcomes of physiological repair (50% mortality at 20 years) [164].

The diverse anatomy of this lesion leads to a significant variance in symptoms and timing of presentation requiring a broad range of treatment options (Figure 29.20). Due to its rarity and the lack of robust data on long term outcomes, comparisons of treatment pathways is made difficult, and decision-making for the surgical management of ccTGA is challenging. The choice of surgical approach will depend on the anatomic features, the patient's age at presentation and severity of symptoms. Center and surgeon preference will also have an impact, given that ccTGA is a rare lesion, consequently most surgeons will not have the opportunity to operate on large numbers of patients; the learning curve for such complex operations is an important consideration. Current data suggests that early anatomic repair is the preferred strategy for the majority of children, with prompt LV banding if required. For patients with a balanced anatomy and no evident dysfunction, expectant management is a viable strategy with transition to other pathways if nonintervention fails [165].

There are numerous surgical approaches for anatomic variations involving ccTGA. These can be classified into three categories according to which ventricle is the designated post-repair systemic ventricle:

- Systemic right ventricle
  - Classical (physiologic) repair
  - Isolated tricuspid valve repair/replacement
  - Multisite pacing
- Systemic left ventricle
  - Senning – ASO (double switch procedure)
  - Senning – Rastelli
- Systemic left and right ventricle

Fontan operation

Physiologic repair

Physiologic repair in ccTGA consists of repair of the associated cardiac defects while maintaining the morphological right ventricle as the systemic ventricle. It addresses VSD closure,

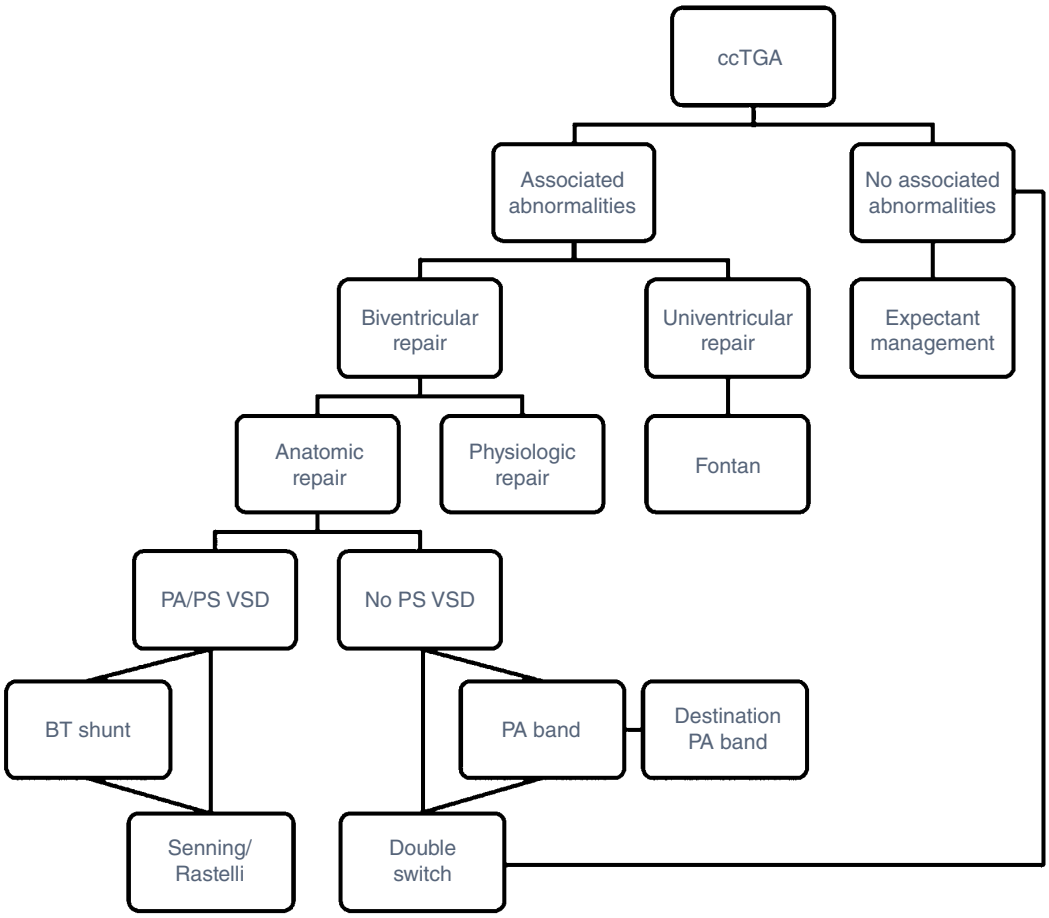


Figure 29.20 Flowchart illustrating anatomical factors determining decision-making in patients with congenitally corrected transposition of the great arteries (ccTGA). PA, pulmonary atresia; PS, pulmonary stenosis; VSD, ventricular septal defect; BT shunt, Blalock-Taussig shunt; PA, pulmonary artery.

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relief of LVOTO, conduit insertion, valvular repair or replacement and pacemaker insertion. Recent data suggests that patients with physiological repair have equivalent short and midterm survival compared to those with anatomic repair [165]. Despite this, physiologic repair appears to be compromised in mid-term outcomes, with progressive RV dysfunction irrespective of TV interventions from 12 years post repair. Overall survival after physiologic repair was 71 vs 80% for anatomic repair at 15 years. In addition to this, interventions to reduce TV regurgitation did not reduce systemic ventricular failure or result in survival benefit [165, 166]. It is noteworthy that these patients also had the highest frequency of transplant among the treatment pathways, indicating that once the systemic ventricle starts to decline there are limited successful treatment options. After physiological repair, close follow-up is required to monitor tricuspid valve function, with early surgical intervention required to repair or replace the TV prior to progressive systemic ventricular failure. Risk factors for poor outcomes include tricuspid valve replacement, preoperative RV dysfunction, complete heart block postoperatively subvalvar PS and "Ebstein-like" abnormity of TV.

Despite these limitations, the physiologic operative approach may still be useful in highly selected cases. Patients with good right ventricular and tricuspid valve function, balanced ventricles, and favorable septation anatomy may be suitable candidates. This is especially the case if a relative contraindication to anatomic repair exists, such as poor mitral valve function, coronary anomalies, small atrium, dextrocardia or inlet VSD features [154].

Anatomic repair

The anatomic repair involves creating AV and VA concordance, ensuring the morphological left ventricle is supplying systemic circulation. Blood is redirected at the atrial level using a Mustard or Senning technique and at the great arteries via the ASO or ventricular level using the Rastelli operation. ASO and Senning procedure (double switch) was first performed in the late 1980s by Imai, Yagihara, Mee, and others [154, 167, 168]. A decade later, Ibawi described an atrial repair in combination with the Rastelli operation for cases of ccTGA with LVOTO and since then, anatomic repairs of both varieties have had a prominent place in the management of ccTGA. Patients will require balanced ventricles and a morphological LV that is capable of maintaining the workload of the systemic circulation. The LV will decondition quickly after birth in patients without pulmonary outflow obstruction or an unrestricted VSD, requiring LV "training." A PA band is placed to increase the afterload of the morphological LV increasing wall thickness [169]. The PA band will also alter the LV/RV pressure ratio, reducing the spherical shape of the RV thus stabilizing tricuspid valve regurgitation [170]. Varying measures are used to ascertain when the LV is ready, it is suggested that a LV-to-RV peak systolic pressure ratio of 0.70 to 0.90 is optimal [171]. Repeat banding may be required to ensure the band is tight enough to adequately train the LV [172]. Periodic assessment by echocardiography, cardiac catheterization, or MRI is used to determine whether adequate training been achieved in advance of anatomic repair. LV training is most successful in younger children, as myocardial response to increased afterload changes from hyperplastic to hypertrophic with increasing age [173].

Patients with a large VSD, LVOTO (subpulmonary or pulmonary stenosis) or pulmonary hypertension expose the morphological LV to systemic pressures from birth, retaining LV mass, and are suitable for primary anatomic repair. An anatomic repair is the preferred approach in patients with good mitral valve function, balanced ventricles and a septatable heart. Patients with poor RV or TV function would also be candidates for this type of repair as physiologic repair in these patients almost always has an unfavorable outcome.

Double switch procedure

The double switch (DS) procedure incorporates an atrial (Mustard or Senning procedure) and an ASO, creating VA and AV concordance. It can be simplified as a three-step procedure.

First, the VSD is closed. Second, the great arteries are switched to their respective ventricles (similar to the ASO performed for D-TGA) and coronaries re-implanted, creating VA concordance. As with the ASO for d-TGA, the identification of coronary anatomy is fundamental to optimal surgical outcome. The mitral valve and the morphological LV become the systemic AV valve and ventricle, and the tricuspid valve and morphological RV become the pulmonary AV valve and ventricle.

Last, the Mustard or Senning part of the operation creates an intracardiac baffle which redirects deoxygenated blood from the RA to the morphological RV via the tricuspid valve, emptying into the neo-pulmonary artery to the lungs. Similarly, the oxygenated blood from the LA is redirected to the LV creating AV concordance. This procedure is appropriate where patients have deteriorating systemic ventricle dysfunction, in the presence of systemic (tricuspid) valve regurgitation. Good LV function and minimal LVOT (pulmonary arterial) obstruction is a prerequisite for this type of surgical repair. Decision-making around surgical timing and patient readiness is complex. Surgical timing is dictated by the severity of CHF symptoms, which is determined by the size of VSD and presence of tricuspid regurgitation (Figure 29.21). The larger the VSD, the more likely that the LV will retain sufficient mass, however, it increases the risk of developing CHF and hence pulmonary hypertension. A PA band can be placed in these patients to minimize pulmonary over-circulation, reducing symptoms of CHF until the child is an adequate weight prior to surgical repair. This is of particular importance due to the technically challenging nature of the operation.

Senning and Rastelli

The combination of the Senning and Rastelli procedures (SR) has been undertaken in patients with ccTGA that have a VSD and significant LVOTO. It involves an atrial level switch (Mustard or Senning procedure) and a Rastelli operation. During the Rastelli operation the VSD is closed with a patch that directs blood to the aorta and a valved conduit is placed between the RV to PA.

Timing of surgery depends on the degree of pulmonary stenosis and cyanosis. Patients with severe pulmonary stenosis or pulmonary atresia require a systemic to pulmonary shunt (e.g. modified BT shunt). The Rastelli procedure can then be performed once the child has outgrown the shunt, which usually happens at around 6 months of age. Patients

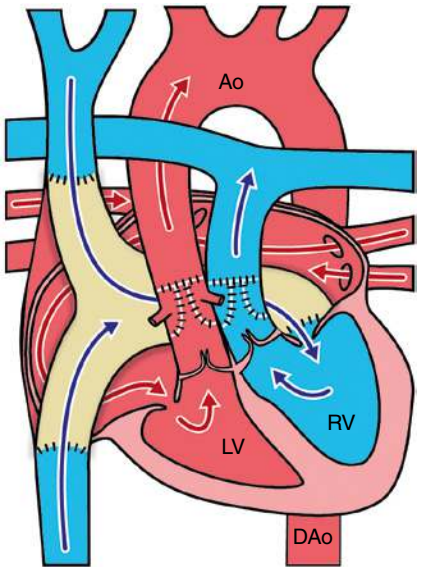


Figure 29.21 "Double switch" operation: Mustard operation with the arterial switch procedure. Ao, aorta; LV, left ventricle; RV, right ventricle; DAo, descending aorta.

with less severe pulmonary stenosis may wait until cyanosis develops but should be performed prior to systemic ventricular failure or tricuspid regurgitation occurs.

Fontan procedure for ccTGA

The use of the Fontan operation as a treatment pathway for ccTGA is controversial. Patients unsuitable for a biventricular repair due to single ventricle physiology (tricuspid atresia) or large VSDs not amenable for septation, are clear candidates for Fontan palliation. However, there is variation in treatment pathways between centers, with patients with Ebstein anomaly, for example, directed to Fontan in some centers and to septation by others. Despite some hesitancy to proceed with a Fontan pathway in potentially septatable, biventricular hearts, there is data to suggest that it compares favorably to physiological biventricular repair [154]. Data regarding the outcome of Fontan vs. other repairs in patients with ccTGA remain limited, but good outcomes in patients with a single ventricle or AV valve support its use in certain patients [165].

Outcomes

From the most current data, anatomic repair offers the best long-term outcomes although it is still unclear which patient cohort will benefit the most (Table 29.6). Early and midterm survival is between 80–85%, with no apparent difference in survival between the DS and SR group [174, 175]. Despite significant early and late interventions, overall survival is approximately 80% at 10 years post anatomic repair [165, 175].

Anatomic repair is based on the principle that long-term outcome is improved when the LV is the systemic ventricle, consequently late LV dysfunction is of particular concern. Late LV dysfunction occurs in approximately 15% of patients after anatomic repair, with a higher risk after the double switch than Rastelli-Senning procedure [175]. This may be due to the increased risk of deterioration of the LV in patients who required LV training [169]. Increased age and the need for pacing are also risk factors for late LV dysfunction, suggesting that early anatomic correction and primary cardiac resynchronization therapy in patients requiring a pacemaker, may reduce the risk of developing late LV failure [176].

Table 29.6 Long-term outcomes after anatomic repair for congenitally corrected transposition of the great arteries

Outcome	Incidence
LV dysfunction	15–20%
Post-op complete heart block	~30%
Neo-aortic valve regurgitation (mild)	70%
Baffle complications	Unknown, 15–50% after d-TGA
Reintervention rate	25%

Conduction abnormalities are common in patients with ccTGA due to abnormal anatomy of the conduction pathway with the risk of complete heart block occurring with a progressive incidence of 2% per year [68]. Post-operative CHB occurs in ~30% of patients, with some data to indicate that it is more common in the DS group especially when VSD closure is required [175, 177]. Centers have been known to advocate for permanent pacemaker lead insertion intraoperatively due to the high risk of heart block associated with ccTGA. Mustard and Senning operations are associated with a significant risk of atrial tachyarrhythmias, which can contribute to LV dysfunction from loss of atrial contraction. Catheter ablation has been used to successfully treat tachyarrhythmias in such patients [178].

Around 70% of patients after DS have at least mild aortic insufficiency (AI). Despite this, mild AI is well tolerated in the majority of patients and does not appear to correlate with morphological LV dysfunction [175]. Previous PA band and use of LeCompte maneuver in side-by-side vessel arrangements may also predispose to AI post-operatively [179].

Despite the Senning procedure being the most commonly used atrial switch technique, there remains no clear data on its long-term advantages over the Mustard technique; both are associated with baffle-complications including stenosis, residual leaks and atrial arrythmias [90]. There is little data on baffle complications after ccTGA; hence, data is inferred from adults after D-TGA repair. One long-term follow-up study showed significant morbidity and mortality after the Mustard procedure for d-TGA and a reintervention rate of nearly 50% [180]. Data in patients with a Senning atrial switch in ccTGA have shown an 11% re-intervention rate for baffle complications. Most baffle complications can now be effectively managed with transcatheter techniques, thus minimizing the need for re-operations [181].

Approximately 25% of patients require some form of reintervention after anatomic repair. Aortic valvular and pulmonary artery interventions were the commonest reinterventions in the double switch group [175]. In the SR group, conduit modifications were the most often required predominantly due to stenosis, calcification, or the need for conduit augmentation [182].

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KEY POINTS: SURGICAL OPTIONS

- RV systemic ventricle after surgery
  - Classical (physiologic) repair
  - Isolated tricuspid valve repair/replacement
- LV systemic ventricle after surgery
  - Senning and ASO (double switch procedure)
  - Senning and Rastelli
- Systemic LV and RV
  - Fontan operation

Anesthetic considerations and perioperative management

Preoperative assessment

The main perioperative risks in patients with ccTGA are tricuspid valve regurgitation, RV dysfunction, congestive cardiac failure, and rhythm abnormalities, including heart block. The pre-anesthetic visit should focus on identifying and risk-stratifying the presence of these, by carefully assessing the patient in terms of history, examination, review of the clinical notes, laboratory results and review of echocardiography, cardiac MRI, and cardiac catheterization. A detailed understanding of what the cardiac defects are, the presence and degree of LVOTO, and the presence of pulmonary vascular occlusive disease and its response to pulmonary vasodilators is vital. History and examination should focus on elucidating symptoms and signs of CHF, systemic valve regurgitation and the presence of cyanosis. Prior procedures such as pacemaker insertion or PAB placement should be noted. Review of the ECG for rhythm and conduction assessment and echocardiography will establish ventricular mass and function as well as systemic AV valve competency. Ventricular mass of the morphological LV is particularly important mainly to check that the LV mass is adequate to become the systemic ventricle. Occasionally a PAB is placed for that purpose and its outcome has to be reviewed.

Induction and maintenance of anesthesia follow the principles highlighted in the section on pathophysiology of ccTGA above. These children may be compromised with little cardiac reserve, so induction has to be tailored to the specific child and the situation. Invasive intraoperative monitoring (arterial line, central venous pressure, and TEE) is necessary, as well as preparation for anesthesia on CPB, as reviewed earlier. Occasionally, preinduction invasive arterial monitoring is indicated, and ability to institute CPB emergently should be available. In the presence of systemic AV valve regurgitation and systemic RV dysfunction, the aim should be to decrease RV pressure load. Care should be taken to control arterial blood pressure and prevent sudden increases in response to intubation or surgical stimulation. At the end of the procedure, TEE should be used to detect residual defects, assess biventricular and valvular function, and evaluate neo-aortic valve regurgitation.

Postoperative course and complications

These children are not candidates for early extubation and will be admitted to intensive care postoperatively for stabilization; therefore, all the invasive monitoring should remain in situ and sedation established. Intracardiac lines measuring right and left atrial pressures are useful in evaluating RV and LV function for management and inotrope titration. In a small proportion of patients in whom the LV fails to function as the systemic ventricle, ECMO, or ventricular assist device might be required as a bridge to recovery.

Selected references

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart

10 Villafane, J., Lantin-Hermoso, M. R., Jenkins, K. J., et al. D-Transposition of the great arteries: the current Era of the arterial switch operation. J Am College Cardiol 2014;64(5):498–511. An excellent summary of "hot topics" by a team of experts on current knowledge of D-TGA including genetics, pre-natal diagnosis, surgical timing, balloon atrial septostomy, intraoperative techniques, coronary obstruction, neoaortic regurgitation and dilation, neurodevelopmental issues, and lifelong care of D-TGA patients.

14 Chiu IS, Anderson RH. Can we better understand the known variations in coronary arterial anatomy? Ann Thorac Surg 2012;94:1751–60. An excellent review with high-quality illustrations and figures presenting the myriad variants of coronary artery anatomy and organizing them in a clear scheme.

21 Rudolph AM. Congenital diseases of the heart: clinical-physiological considerations, (3rd edn.) Chichester, England: Wiley-Blackwell, 2009. Detailed description of intercirculatory mixing in different D-TGA morphologies.

37 Rashkind WJ, Miller WW. Creation of an atrial septal defect without thoracotomy: a palliative approach to complete transposition of the great arteries. J Am Med Assoc 1966;196:991–2. The classical paper describing the rationale, technique, and outcomes for the balloon atrial septostomy, a procedure that continues to be performed in a significant number of transposition patients to this day.

50 Sarris GE, Balmer C, Bonou P, et al. Clinical guidelines for the management of patients with transposition of the great arteries with intact ventricular septum. Cardiol Young 2017;27(3):530–69. Comprehensive guidelines by The Task Force on Transposition of the Great Arteries of the European Association for Cardio-Thoracic Surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC). The guidelines are intended to facilitate safe and effective perioperative care based on review of the published evidence.

58 Lim JM, Porayette P, Marini D, et al. Associations between age at arterial switch operation, brain growth, and development in infants with transposition of the great arteries. Circulation (New York, N.Y.) 2019;139(24):2728–38. Study looking at risk factors for brain injury and outcomes in 45 infants after ASO demonstrating surgery beyond 2 weeks of age is associated with impaired brain growth and slower language development.

72 Fricke TA, Buratto E, Weintraub RG, et al. Long-term outcomes of the arterial switch operation. J Thorac Cardiovasc Surg 2021;163(1):212–9. A large single-center experience with 844 patients reporting long term outcomes after ASO from 1983 to 2015. Overall long-term outcomes for ASO are good, with excellent late survival and functional status. However, reintervention is common with 15% having at least moderate AR or had undergone neoaortic valve replacement at 25 years.

107 Bellinger DC, Wypij D, Rivkin MJ, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neurophysiological assessments and structural brain imaging. Circulation 2011;124:1361–9. A very important follow-up study from the Boston Circulatory Arrest cohort, demonstrating long-term neurodevelopmental problems in many of the early arterial switch neonates.

139 Samuel R, Froese N, Betts K, Gandhi S. Intraoperative extubation post arterial switch operation for transposition of the great arteries with intact ventricular septum: a one-year, single center experience. Semin Thorac Cardiovasc Surg 2021;33(1):134–40. A small, preliminary retrospective review of intraoperative extubation post ASO for neonates with TGA/IVS, demonstrating it is safe.

165 Barrios PA, Zia A, Pettersson G, et al. Outcomes of treatment pathways in 240 patients with congenitally corrected transposition of great arteries. J Thorac Cardiovasc Surg 2021;161(3):1080–93. A large retrospective review of 240 patients with ccTGA from the Cleveland Clinic looking at outcomes for different treatment pathways. The study concluded that early anatomic repair fares better than physiologic repair and patients managed expectantly show what appears to be excellent survival. Physiologic repair is compromised by progressive RV dysfunction that escalates at 12 years post-repair.

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CHAPTER 30

Anesthesia for the Patient with a Single Ventricle

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Introduction

In the early 1970s, Fontan and Baudet [1] and Kreutzer et al. [2] independently described the operative treatment of tricuspid atresia (TA) that resulted in nearly normal systemic arterial oxygen saturation and normal volume work for the single functional systemic ventricle. This procedure subsequently referred to as the Fontan operation, created a series circulation that requires the single ventricle (SV) to pump fully saturated blood only to the systemic circulation, thereby reducing the pressure and volume work to that of a normal systemic ventricle. Systemic venous drainage passes directly through the pulmonary vascular bed without the benefit of a pumping chamber, and pulmonary vascular resistance (PVR) must be low to maintain the pulmonary circulation and the cardiac output (CO) on which it depends. The principle of the Fontan operation has subsequently been applied to the full spectrum of cardiac lesions with one functional ventricle. Suitable physiology for ultimate palliation with a modification of the Fontan procedure is predicated on appropriately timed and executed staged operations designed for the specific patient's SV physiology. Essentially, all patients with a single functional ventricle now undergo staged palliation, resulting in the completion of the Fontan circuit at 18 months to 4 years of age. The majority undergoes a neonatal palliative procedure, followed by a superior cavopulmonary connection (bidirectional Glenn or hemi-Fontan procedure) at 3–6 months of age in all patients. This chapter will initially present these principles by using hypoplastic left heart syndrome (HLHS) as the most common SV congenital cardiac lesion. Tricuspid atresia and other forms of SV lesions will then be discussed. Finally, the growing recognition of the implications and sequelae of the long-term Fontan circulation, along with management strategies, will be described.

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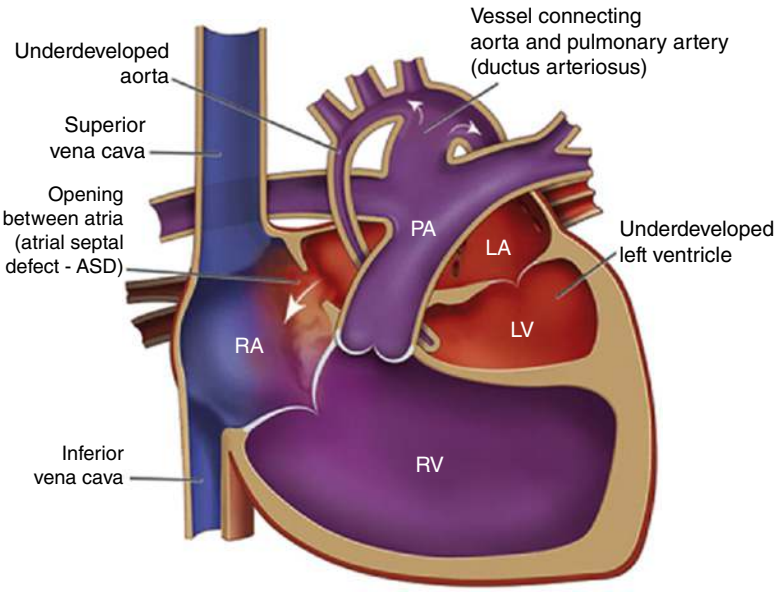


Figure 30.1 Hypoplastic left heart syndrome. This diagram depicts mitral stenosis and aortic atresia. ASD, atrial septal defect; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PA, pulmonary artery. (Source: Metcalf & Rychik [6]. Reproduced with permission of Elsevier.)

Hypoplastic left heart syndrome

Incidence, anatomy, and natural history

Hypoplastic left heart syndrome (HLHS) represents the fourth most common defect presenting in the neonatal period and accounts for 7.5% of newborns with congenital heart disease (CHD) requiring early therapeutic intervention. Although the incidence of HLHS is 1.4–3.8% of all CHD, it results in 23% of deaths from CHD within the first week of life and 15% within the first month [3]. HLHS has a high heritability component, inherited as a complex trait causing a severe form of valve malformation. Thus, it is important to screen first-degree relatives of HLHS patients [4]. Recent genome sequencing has demonstrated a link between gene defects causing HLHS and those causing cardiomyopathies. Clinically, certain variants associated with these genes could increase the risk of developing myocardial dysfunction in HLHS patients [5].

HLHS is characterized by a single right ventricle (RV) and varying degrees of hypoplasia of the left side of the heart. Most commonly HLHS involves either severe aortic stenosis (AS) or aortic atresia (AA), severe mitral stenosis (MS) or mitral atresia (MA), and a very hypoplastic or rudimentary left ventricle (LV) (Figure 30.1) [6, 7]. Blood returns normally from the pulmonary veins to the left atrium (LA), but obstruction at the mitral and aortic levels means that the majority of flow must be left-to-right across the atrial septum. This causes enlargement and dilation of the right atrium (RA) and RV, which must support the outputs of both the systemic and pulmonary circulations. Blood flows from the pulmonary artery (PA) right-to-left through the patent ductus arteriosus (PDA) to the aorta, thus supplying the systemic arterial circulation. Although there may be some antegrade flow through the aortic valve, perfusion of the brachiocephalic vessels, aortic root, and coronary arteries occurs mainly via retrograde flow from the PDA into the ascending aortic arch – a hallmark of HLHS. Some variations of left heart hypoplasia involving the LV, mitral valve (MV), and aortic valve (AV) may be amenable to two-ventricle surgical repairs and are presented in detail in Chapter 27.

Without intervention, HLHS is uniformly fatal in the first several months of life. As the PDA narrows and closes, diminished blood flow to the systemic circulation and coronary arteries results in a state of circulatory shock resulting in poor perfusion, lactic acidosis, and respiratory failure.

Pathophysiology of HLHS

A parallel circulation exists in HLHS. Both pulmonary and systemic venous blood mix in the RA, and the RV, via the PA, then supplies both the pulmonary circulation (through the branch PAs) and the systemic circulation (through the PDA). Prostaglandin E_1 infusion must be initiated after birth to maintain patency of the ductus arteriosus. Maintenance of a delicate balance between pulmonary (Qp) and systemic (Qs) blood flow is necessary, with the Qp: Qs optimally kept near 1: 1 to maintain adequate perfusion of lungs and body. As pulmonary vascular resistance (PVR) decreases after birth, Qp: Qs increases and may reach 2: 1 or 3: 1. The resultant pulmonary overcirculation at the expense of the systemic circulation generally results in pulmonary interstitial and alveolar edema, tachypnea, and retractions, potentially culminating in respiratory failure. Increases in FiO_2 or hyperventilation will further lower PVR and should be avoided. Even more critical is the "steal" effect, in which blood flow is diverted away from the systemic circulation, compromising flow to both the body and the coronary arteries. Cardiogenic shock can ensue, with poor perfusion and increasing lactic acidosis. Steal of flow from the systemic circulation may also result in mesenteric ischemia and necrotizing enterocolitis. Maneuvers to increase PVR are important treatment strategies if steal is suspected. These strategies can include maintaining FiO_2 at 0.21 and allowing $PaCO_2$ to rise via

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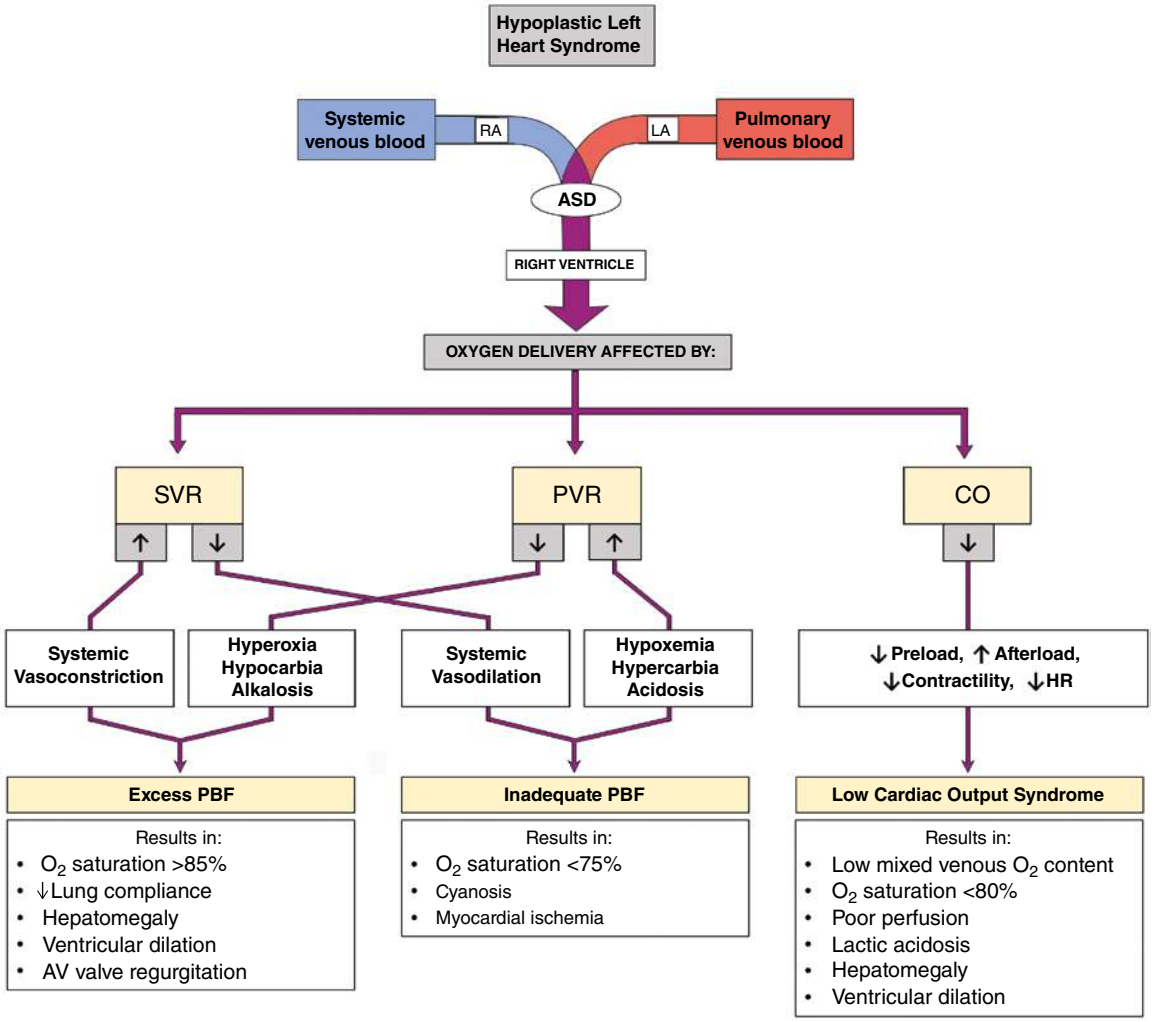


Figure 30.2 Pathophysiology of the functional single systemic ventricle. Optimal oxygen delivery involves maintaining adequate cardiac output while balancing SVR and PVR. SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; PBF, pulmonary blood flow; AV, atrioventricular; HR, heart rate; PCO_2, partial pressure of carbon dioxide; PO_2, oxygen tension.

spontaneous respiration or by decreasing minute ventilation for mechanically ventilated patients. The former practice of delivering sub-ambient FiO_2 via mechanical ventilation can reduce both systemic and cerebral oxygenation significantly but has been abandoned in favor of maintaining spontaneous respirations preoperatively and early surgical intervention [8]. Should the PDA narrow, Qp: Qs increases and systemic perfusion becomes compromised, leading to a cardiogenic shock.

Anatomic variables can have a major impact on the observed physiology. If the ASD is restrictive or limited to a patent foramen ovale (PFO), resistance to pulmonary venous return may balance pulmonary and systemic resistances, positively impacting Qp: Qs. Infants who lack that restriction, such as those with a large atrial septal defect (ASD) or unrestrictive anomalous pulmonary venous return, tend to exhibit high Qp: Qs. However, infants presenting with an intact atrial septum and no alternative decompressing vein have severely obstructed pulmonary venous return, leading to left atrial hypertension and an extremely low Qp: Qs. These infants exhibit marked hypoxemia and require intervention to enlarge the atrial communication and decompress pulmonary venous return in order to have any chance of survival. This may be accomplished either via *in utero* atrial septostomy or immediately after planned delivery in an adjacent operating room (OR) via an *ex utero* intrapartum treatment (EXIT) procedure [9, 10]. Several other factors, including atrioventricular valve regurgitation (AVVR) and hemoglobin level, can also affect the pathophysiology of HLHS. An overview of SV pathophysiology is presented in Figure 30.2.

In the current era, the majority of HLHS cases are diagnosed *in utero* after an abnormal screening ultrasound at 18–22 weeks' gestation is confirmed by a detailed cardiac examination. Fetal echocardiography can also reveal additional features including limitation of flow across the atrial septum and abnormal pulmonary venous return flow patterns which, if present, can greatly impact risk and survival [10]. In the Single Ventricle Reconstruction Trial (SVRT), a multicenter study of over 500 HLHS patients sponsored in the US and Canada by the Pediatric Heart Network of the US National Heart, Lung, and Blood Institute, 76% of HLHS

patients were diagnosed *in utero* [11]. As noted, fetal catheter interventions may be attempted for some HLHS patients, either to dilate and stent a restrictive atrial septum or to dilate the aortic valve. An analysis from the International Fetal Cardiac Intervention Registry that examined fetuses with HLHS from 13 institutions between 2001 and 2015 demonstrated a 77% success rate with atrial septoplasty and atrial stent placement procedures. However, complications, including 13% fetal demise, were common [9]. Fetal interventions are discussed in detail in Chapter 19.

Although prenatal diagnosis alone has not been demonstrated to improve HLHS survival, late postnatal diagnosis and distance from a cardiac surgical center negatively impact survival, with most mortality occurring before surgical intervention [12]. Therefore, prenatal diagnosis and planned delivery in or near a cardiac surgery center may improve survival. Late diagnosis occurs when the PDA narrows and the infant demonstrates clinical signs of low CO and shock, prompting echocardiographic assessment. Emergent resuscitation of the infant, including immediate initiation of a PGE_1 infusion, is essential for survival. The magnitude and the type of acquired vital organ dysfunction usually correlate with the degree of circulatory instability at the time of diagnosis. Infants who have suffered a profound or protracted shock state can demonstrate a wide spectrum of injury to renal, central nervous system, cardiac, gastrointestinal, or hepatic systems [13–15]. These derangements may necessitate a delay in operative intervention to permit recovery. Because 15–30% of HLHS neonates also have extracardiac anomalies or genetic syndromes such as the CHARGE association or chromosomal abnormalities, a thorough evaluation for these problems should also be performed [3].

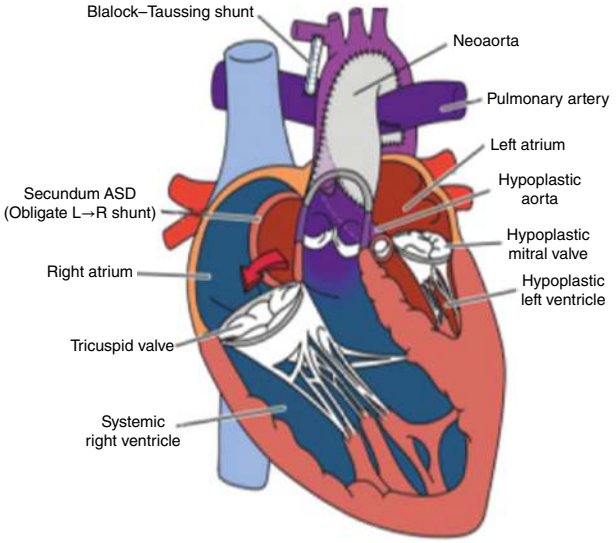


Figure 30.3 Norwood Stage I palliation for hypoplastic left heart syndrome. See text for details. (Source: Berenstain & Spaeth [18]. Reproduced with permission of Cambridge University Press.)

Surgical and transcatheter approaches and outcomes

Stage I palliation

In 1979, Norwood et al. reported a neonatal palliative operation for HLHS that stabilized native HLHS physiology and eliminated ductal dependence. He later described a Fontan palliation as the second stage operation, resulting in the first long-term survivors of HLHS [16]. The Norwood stage I palliation involves reconstruction of the diminutive ascending aorta, usually with a cryopreserved homograft patch, along with the creation of outflow from the systemic RV through the pulmonary valve, which also provides blood flow to the native aortic root and coronary arteries. The pulmonary valve becomes the "neo-aortic valve" (Figure 30.3) [17, 18]. The main PA is transected, and the proximal portion of the PA is incorporated into the aortic repair while the underside of the PA bifurcation is oversewn. In addition, an atrial septectomy is performed to provide unrestricted left-to-right blood flow across the atrial septum. Pulmonary blood flow is then delivered via a polytetrafluoroethylene (PTFE) shunt, either via the creation of a systemic-to-pulmonary shunt from the right innominate or subclavian artery to right PA (also termed modified Blalock–Thomas-Taussig shunt [mBTTS]) or by the creation of an RV–PA shunt (also termed the Sano shunt). It is crucial that the area of the anastomosis between the pulmonary valve and the aortic valve is free of obstruction, as it can affect the already tenuous coronary blood flow. The complete removal of any residual ductal tissue to prevent later coarctation of the aorta is also critical. During aortic arch reconstruction, cardiopulmonary bypass (CPB) techniques must provide a bloodless surgical field. Deep hypothermic circulatory arrest (DHCA) or antegrade regional cerebral perfusion (ACP) may be utilized for this purpose. Preference for a particular approach is largely surgeon and institution dependent. Details of each technique along with short- and long-term outcomes are discussed in Chapter 11.

Systemic-to-pulmonary and RV-to-pulmonary shunts

The systemic-to-pulmonary artery shunt is a 3.0- to 4.0 mm polytetrafluoroethylene (PTFE) graft that provides continuous flow into the PA. Originally described as a modified "Blalock-Taussig" shunt after surgeon Alfred Blalock and cardiologist Helen Taussig, more recently, it has become identified as a modified "Blalock-Thomas-Taussig shunt" to recognize the primary contribution of Vivien Thomas, a surgical technologist, to its successful development and implementation [19, 20]. Shunt flow is inversely proportional to the length of the shunt and the fourth power of its radius. It is directly proportional to the pressure drop across the shunt and therefore influenced by the ratio of PVR and systemic vascular resistance (SVR). Kinking or distortion of either the shunt or PA can occur and interfere with the flow. Because there is continuous "run-off" of flow from the systemic circulation into the PA, these patients remain at risk for steal from the systemic circulation as PVR decreases. This is proposed as the major pathophysiological etiology for the frequent instability observed in the early postoperative period in these patients. In 2003, Sano et al. reported improvement in stage I survival in a small number of patients at one institution when pulmonary blood flow (PBF) was provided by a

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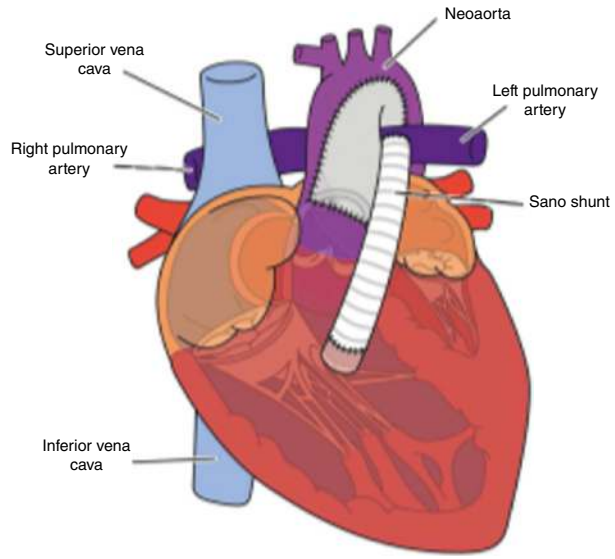


Figure 30.4 Norwood Stage I palliation for hypoplastic left heart syndrome with right ventricle to pulmonary artery shunt (Sano shunt). See text for details. (Source: Berenstain & Spaeth [18]. Reproduced with permission of Cambridge University Press.)

5–6 mm PTFE graft from the RV to the PA, rather than via an mBTTS (Figure 30.4) [18, 21]. Because the RV–PA shunt arises proximal to the neo-aortic valve, there is no flow from the aorta into the PAs during diastole, limiting diastolic run-off and coronary ischemia. The resultant higher diastolic blood pressure has been hypothesized as the physiologic reason for improved survival.

The SVRT was designed to test the hypothesis that stage I survival would improve with the utilization of the RV–PA shunt, with an endpoint of death or transplantation in the first 12 months [7]. In all, 555 infants were randomized to receive either an mBTTS or RV–PA shunt. Approximately 10% of subjects required cross-over from their randomly assigned shunt type to the other shunt type because of anatomic considerations. At 12 months, 36.4% of the mBTTS subjects had died or been transplanted, compared with 26.3% for the RV–PA shunt ($P = 0.010$). However, overall complication rates in the RV–PA shunt group were higher (72 vs. 46 per 100 infants, $P = 0.03$), and the number of infants experiencing one or more complications was also greater with the RV–PA shunt (39 vs. 28%, $P = 0.03$). After 12 months, the hazard ratio for death or transplantation did not differ between the two types of shunts. Follow-up after 6 years demonstrated slightly higher transplant-free survival (5%) but an increased need for catheter re-interventions in the RV-PA shunt patient group; however, there were no statistically significant differences in the hazard ratio for death or transplantation as well as catheter re-interventions [22]. A recent meta-analysis of 32 studies by Cao et al. assessed long-term survival in HLHS with either mBTTS ($n = 1348$) or RV-PA shunt ($n = 1258$). Although the RV-PA shunt group had significantly higher in-hospital survival and inter-stage survival between stage I and II palliation until 2 years post-stage I palliation, no significant differences in long-term outcomes between stage II and stage III palliation were identified [23]. In contemporary practice, the shunt type used depends largely on the surgeon and institutional preference.

In a publication specifically examining the rate and causes of 30-day in-hospital mortality in SVRT subjects, 16% of patients died during the initial hospitalization, with 12% mortality in the first 30 days after Norwood stage I palliation. Although after multivariable analysis shunt type was not identified as a significant risk factor for mortality, the presence of an mBTTS was an independent risk factor for cardiopulmonary resuscitation (CPR). Independent risk factors for both 30-day and total in-hospital mortality included low birth weight, genetic abnormality, post-procedure need for extracorporeal membrane oxygenation (ECMO), and open sternum. Longer duration of DHCA was an independent risk factor for hospital mortality. Independent risk factors for major morbidity (renal failure, sepsis, increased duration of ventilation, and hospital stay) included genetic abnormality, lower center/surgeon volume, open sternum, and additional post-Norwood operations [24].

Inter-stage mortality occurring after the initial hospitalization for stage I palliation and during the 3–6 months prior to Stage II superior cavopulmonary connection (SCPC) has been a persistent issue. The physiology of the HLHS patients remains tenuous after the initial palliation, as a parallel circulation with all systemic and pulmonary output passing through the single systemic ventricle still persists. The Qp: Qs remains labile, and thus, coronary ischemia continues to be a risk. Significant hemodynamic perturbations may easily result from dehydration due to viral gastroenteritis, upper respiratory infections, or micro-aspiration episodes caused by a recurrent laryngeal nerve injury that frequently accompanies stage I palliation. In the SVRT, of 426 subjects discharged from the hospital, 50 died inter-stage (12%) [25]. The inter-stage death rate was greater for mBTTS patients (18%) than for RV–PA shunt patients (6%, $P < 0.001$). Risk factors for inter-stage death included gestational age <37 weeks, Hispanic ethnicity, AA/MA, a greater number of post-Norwood complications, census block poverty level, and moderate to severe AVVR. Ahmed et al. recently developed a validated risk scoring system to predict mortality or transplant in single-ventricle patients during the inter-stage period between stage I and II palliation. Between 2008 and 2015, data from over 2,000 patients from the National Pediatric Cardiology Quality Improvement Collaborative Registry were analyzed to create a weighted scoring system. This novel system, known as the NEONATE score, assessed the following independent risk factors: Norwood type (mBTTS or hybrid vs. Sano shunt), postoperative ECMO, opioids required at discharge, no digoxin required at discharge, arch obstruction, ≥ moderate Tricuspid regurgitation, and extra oxygen plus ≥ moderate tricuspid regurgitation at discharge. During the inter-stage period, the strongest predictor of death or transplant was ≥ moderate tricuspid regurgitation, which worsened if oxygen was required [26]. With a combined 28% mortality observed in the SVRT in the inter-stage period between stages I and II, the challenges of caring for this group of patients are evident. Death after stage II SCPC in the first year of life is less common; the stabilizing effect on the pathophysiology of HLHS (see later) is the most significant factor.

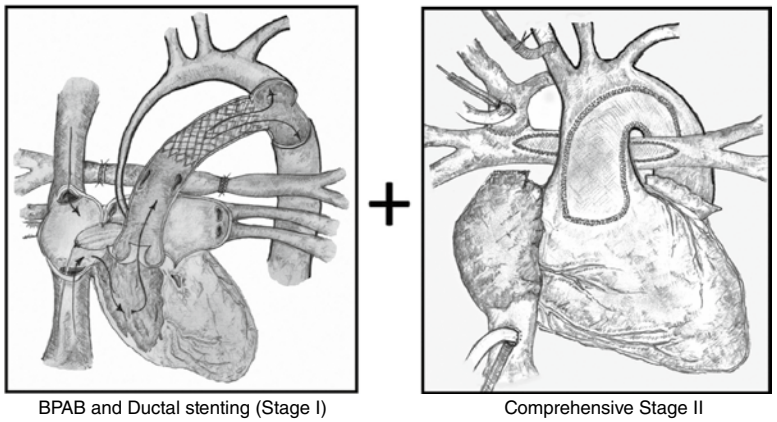


Figure 30.5 Giessen hybrid procedure for HLHS: stage I and stage II. Giessen hybrid procedure consists of bilateral pulmonary artery banding with ductal stenting in the neonatal period and comprehensive stage II procedure in the infancy period. The arrows show the direction of the bloodstream. BPAB, bilateral pulmonary artery banding. (Source: Yörüker & Akintürk [33]. Reproduced with permission of Elsevier.)

Hybrid procedure

Despite continuing improvements in the perioperative management of infants with HLHS, specific populations of patients remain at higher risk and demonstrate a more significant level of morbidity and mortality during and after surgical stage I palliation [27]. Risk factors include birth weight <2.5 kg, prematurity, ascending aortic size <2 mm, MS/AA anatomy, poor RV function, severe tricuspid regurgitation, restrictive atrial septum, obstructed pulmonary venous return, and the presence of additional cardiac or non-cardiac anomalies [28–32]. Continuing advancements in interventional cardiology techniques have facilitated the development of alternative therapeutic strategies for these subpopulations of patients. Due to the utilization of both surgical and interventional catheterization procedures, these interventions are known as "hybrid" procedures. A hybrid procedure is performed in the catheterization laboratory, OR, or "hybrid" procedure suite. It consists of median sternotomy without CPB, surgical placement of bilateral PA bands, and placement of a stent in the PDA by interventional cardiology via access obtained in the main PA (see Figure 30.5) [33–35]. The atrial septum can also be stented if restrictive. Advantages of hybrid procedures include avoiding CPB and/or DHCA in the neonatal period and providing an extended waiting period for infants who require cardiac transplantation or who may be eligible for biventricular repair. The hybrid procedure may also be utilized to delay a planned Norwood operation or as a salvage procedure for patients unsuitable for early Norwood operation [35]. The hybrid procedure is further detailed in Chapter 34. Modifications to the hybrid procedure continue to occur as newer devices become available. One such example is the internal self-expanding flow restrictor, which can be utilized in place of external, surgically placed PA bands, allowing all components of the hybrid procedure to be accomplished in the catheterization laboratory [36].

As with surgically palliated patients, inter-stage mortality continues to be an issue after the hybrid procedure. Close echocardiographic monitoring for tricuspid valve regurgitation and/or RV dysfunction has been advocated, as these can indicate obstruction at the atrial level or through the PDA stent. Re-interventions in the catheterization laboratory are not infrequently required to relieve such obstructions [37]. The most concerning and potentially life-threatening complication involves the development of reverse or pre-ductal coarctation, resulting in diminished coronary and cerebral perfusion. This can occur either secondary to uncovered ductal tissue that remains capable of closure or as a result of ductal stent placement. Once recognized, additional retrograde stent placement is utilized to address proximal aortic arch obstruction [38].

At the age of 3–6 months, aortic reconstruction, along with removal of the PA bands, ductal and atrial stents, repair of the PAs (if necessary), atrial septectomy, and SCPC, is performed. This is known as a "comprehensive stage II procedure" (See Figure 30.5). Patients subsequently progress to Fontan completion via a surgical approach or placement of a covered stent via catheter intervention [33, 39].

While previous small studies demonstrated no significant difference in survival statistics between the hybrid and traditional Norwood stage I palliation [40–43], a 2018 meta-analysis of 14 studies comparing outcomes found that the hybrid group had significantly higher early mortality, reduced 6-month and 1-year transplant-free survival rates, and an increased number of required re-interventions [44]. However, some institutions preferentially perform hybrid procedures with outcomes comparable to those seen with the Norwood procedure [33, 44, 45]. According to the Society of Thoracic Surgeons Congenital Heart Surgery Database, 13 out of 100 institutions performed >50% of stage I palliations as a hybrid rather than Norwood procedure between 2010 and 2012 [46]. With continuing experience and technical modifications, the hybrid procedure may offer the potential for increased survival opportunity with early avoidance of CPB for certain groups including high-risk patients, those awaiting cardiac transplantation, and those with the potential for future biventricular repair [47].

Biventricular repair in borderline HLHS

Given the broad spectrum of pathology observed in HLHS, with LV size ranging from rudimentary to mildly hypoplastic, the best surgical strategy may not always be clear. Patients

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with "borderline HLHS," also known as "hypoplastic left heart complex," or a "borderline LV" often pose particular management challenges, as either single-ventricle palliation or a biventricular repair may be considered [48, 49]. In recent years, strategies to aid in determining which patients may be suitable for biventricular repair have been developed using echocardiographic and cardiac MRI parameters. While the use of these parameters may differ between institutions, mitral and aortic valve Z-scores (Z-score is standard deviation; e.g., a -2 Z score for a valve diameter is 2 standard deviations below normal for weight or body surface area) of between -5 and -2 (excluding atretic valves) are typical. Other critical factors include LV end-diastolic pressure, LV end-diastolic volume index, LV length and volume, and the degree of endocardial fibroelastosis (EFE) [50]. A group of 24 Congenital Heart Surgeons Society institutions studied 320 neonates who underwent either Norwood palliation or biventricular repair, leading to the development of hazard models based on various morphologic and functional characteristics [51].

Due to the high risk associated with the primary neonatal biventricular repair, many institutions choose a period of LV recruitment or staged LV rehabilitation, with initial SV palliation. This relieves obstructions and promotes PBF. Other techniques to stimulate LV growth, such as resection of endocardial fibroelastosis (EFE), mitral and/or aortic valvuloplasty, and ASD restriction, are also performed. Additionally, increasing PBF (via an mBTTS plus SCPC versus an RV-PA shunt) after ventricular septation volume loads the LV and stimulates growth. If these techniques successfully promote adequate LV growth, subsequent takedown of the SV palliation with conversion to a biventricular repair can occur [50, 52].

The success of biventricular conversion or repair is dependent on many factors, including appropriate patient selection and clinical and technical experience. Further evidence comparing long-term outcomes between biventricular conversion versus progression with single-ventricle physiology to Fontan completion is still being gathered [53].

Anesthetic considerations

Preoperative considerations

The diagnosis of HLHS is most frequently made *in utero*. After an initial assessment, immediate treatment in the delivery room for HLHS patients includes initiation of a PGE_1 infusion, placement of umbilical arterial and venous catheters, maintenance of spontaneous ventilation on room air, and transfer to a neonatal or cardiac intensive care unit (ICU). A postnatal transthoracic echocardiogram is performed to confirm the initial diagnosis and provide other crucial anatomic information, including LV size, presence of AVVR, degree of atrial septal restriction, or the presence of anomalous pulmonary venous return. Other less common but important details such as the presence of coronary artery fistulae or sinusoids to the LV should also be assessed. Patients with a restrictive atrial septum may require urgent or emergent intervention, requiring either balloon atrial septostomy or early surgical intervention. Cardiac catheterization is rarely performed for diagnostic purposes, and additional imaging (i.e., computed tomography [CT] or magnetic resonance imaging [MRI]) is seldom required unless anatomic questions remain. Certain anatomic and physiologic features have been identified as risk factors that may affect outcomes (see Table 30.1).

Table 30.1 Preoperative risk factors prior to stage-1 palliation

Mitral stenosis/aortic atresia
Hypoplastic ascending aorta (<2 mm)
Restrictive atrial septum
Obstructed pulmonary venous return
Greater than moderate tricuspid valve regurgitation
Pulmonary valve regurgitation
Age >14 days
Pre-maturity
Low birth weight (<2.5 kg)
Non-cardiac congenital abnormalities
Metabolic acidosis
Chromosomal abnormalities
Inotropic support
Right ventricular dysfunction

Source: Roeleveld et al. [28]. Reproduced with permission of Cambridge University Press.

The chest radiograph is followed daily to assess the heart size and status of the pulmonary vasculature. Common preoperative laboratory tests include complete blood count, coagulation studies, and blood type and cross-match, along with the measurement of serum electrolytes, blood urea nitrogen, creatinine, and glucose. In a recent evaluation of standard preoperative laboratory testing for pediatric cardiac surgery patients in the US and Canada by the Congenital Cardiac Anesthesia Society Hemostasis Interest Group, 11 of 12 centers surveyed reported routinely obtaining preoperative testing. However, 83% agreed that only a type and screen and complete blood count were necessary. No centers reported changes in management due to preoperative testing, suggesting that preoperative testing requirements are controversial and subject to institutional preferences [54].

Ideally neonatal HLHS patients "self-regulate" their Qp:Qs prior to stage I palliation, spontaneously breathing with a slightly elevated $PaCO_2$. Diuretics are often used preoperatively to limit blood volume recirculating through the lungs. Nasal continuous positive airway pressure (CPAP) may be helpful to provide positive pressure to relieve respiratory distress and elevate the PVR while maintaining spontaneous respiration. Tracheal intubation and mechanical ventilation are reserved for the most severe cases of respiratory insufficiency or for patients with anatomic variants (e.g., restrictive intra-atrial communication) that markedly diminish PBF. Early surgical intervention before severe derangements in Qp:Qs ensue is essential to prevent complications.

Intraoperative considerations

Neonates presenting for stage I reconstruction (i.e., Norwood procedure with mBTTS or Sano shunt) receive an intravenous (IV) induction of anesthesia with meticulous attention to the hemodynamic consequences of the anesthetic agents selected. Phenylpiperidine-based synthetic opioids, such as fentanyl, are generally preferred because they blunt the

endogenous catecholamine response to noxious stimuli at doses that are usually tolerated hemodynamically [55–57]. However, even with these hemodynamically "neutral" agents, larger doses may result in significant cardiovascular changes, such as bradycardia and hypotension. These observations suggest that some endogenous catecholamine release is required in an infant with HLHS to sustain satisfactory hemodynamics. Unfortunately, the threshold narcotic dose that is "sufficient" and not "excessive" varies between patients, necessitating careful titration.

Although clinical research conducted in the early 1990s popularized the view that very high doses of opioid analgesics should be administered perioperatively for stress hormone suppression in neonates undergoing cardiac surgery [58], efforts to duplicate these findings have not confirmed the original results [59]. The latter demonstrated that very high doses of fentanyl did not completely suppress the release of endogenous catecholamines, even in combination with benzodiazepine infusions. Additionally, outcome measures were no different in any of the study groups. Emerging evidence has demonstrated potential benefits of the use of dexmedetomidine in pediatric cardiac surgery, including neuroprotection as well as improved morbidity and mortality [60]. According to data from the Congenital Cardiac Anesthesia Society and Society of Thoracic Surgeons Cardiac Anesthesia Database Collaboration, dexmedetomidine use has steadily increased since 2010 [61]. Strategies vary significantly between institutions, with total intraoperative fentanyl doses ranging between 10–100 μg/kg, and the addition of low-dose volatile anesthetics, benzodiazepines, ketamine, and dexmedetomidine in various combinations described as components of a balanced anesthetic approach to initial palliations for HLHS [62]. Most institutions now utilize fentanyl dosages in the lower range, generally <25 μg/kg.

Management of the airway and ventilation assumes great importance during induction of anesthesia. Given the propensity for most neonates with HLHS to have excessive PBF, the anesthesiologist must take care not to employ ventilatory maneuvers that lower PVR, such as hyperventilation or utilization of high inspired concentrations of oxygen (FiO_2). In an infant with typical HLHS physiology, manual ventilation should be initiated with room air or a low concentration of supplemental oxygen. The extent to which FiO_2 is increased before laryngoscopy should depend upon the magnitude of hemodynamic response to the initiation of controlled ventilation. Infants who demonstrate a significant reduction in systemic arterial pressure despite low FiO_2 may not tolerate prolonged exposure to a higher FiO_2 without deleterious hemodynamic consequences.

Intraoperative monitoring consists of standard cardiovascular, respiratory, and temperature monitors and continuous direct arterial pressure monitoring. An umbilical arterial line, if present, may be used to preserve other arterial access sites for future interventions. Most centers utilize central venous access as well. An umbilical venous catheter positioned in the orifice of the superior vena cava (SVC) at the time of surgery serves as a valuable monitor of mixed venous oxygen saturation, enabling more precise assessment of systemic CO and Qp: Qs [6, 63, 64]. Some institutions may place direct transthoracic atrial lines instead of percutaneous jugular or subclavian central venous pressure catheters due to concern regarding thrombosis in the central thoracic veins in SV patients. However, other institutions have failed to demonstrate the significant risk associated with the use of upper body central venous catheters even in SV patients [65]. Peripherally inserted central catheters (PICCs) are increasingly utilized as well. In a 2020 retrospective review of PICC use in pre-stage II SV patients, only 2 out of 56 patients with PICCs developed detectable thrombus (4%) versus 3 out of 17 patients with central venous catheters (18%) [66]. Most centers utilize cerebral and somatic near-infrared spectroscopy (NIRS) as additional non-invasive monitors which correlate with SvO_2. Cerebral NIRS can be used to guide ACP as it has been shown to detect alterations in CBF in neonates undergoing Norwood stage I palliation [67, 68]. The use of cerebral and somatic NIRS in the immediate postoperative period has also been shown to predict early mortality and to highlight the need for ECMO in HLHS patients [69]. Transesophageal echocardiography (TEE) is often utilized depending on the size of the neonate and institutional preference. Epicardial echocardiography after CPB can also be utilized and is particularly useful to assess AVVR and neo-aortic regurgitation.

Measures to clear airway secretions and assure complete re-expansion of the pulmonary parenchyma are performed in the terminal phases of rewarming on bypass. The magnitude of reduction in the mean systemic arterial pressure that occurs with the opening of the shunt during the terminal phase of CPB can provide qualitative insights into what PVR might be expected in the early post-CPB period. Initial ventilatory support should be adjusted accordingly. It is best to begin with a FiO_2 between 0.6 and 1 and a pattern of ventilation designed to result in low-normal $PaCO_2$, recognizing that further adjustments will be indicated by the individual infant's physiology. Assuming a technically satisfactory repair without unusual risk factors, PVR typically falls within the first few hours after surgery. Until then, some patients may potentially require high levels of supplemental oxygen in the immediate post-CPB period.

While the physiologic goals post-CPB remain identical to those of the preoperative period, the variables affecting the achievement of these goals differ. The pulmonary circulation now resides either at the distal end of a restrictive prosthetic systemic-to-pulmonary shunt or an RV–PA shunt. A variety of subtleties, including technical execution of the shunt, relief of atrial obstruction, and the pre-existing condition of the pulmonary circulation, can render the ultimate physiology unpredictable. When a Sano shunt has been performed, technical issues of graft insertion, proper graft size (particularly in the neonate <2.0 kg), and the ability to delineate the etiology of insufficient PBF at the termination of CPB can introduce additional complexities.

Even with a perfect technical result, the Norwood operation does not reduce the volume or pressure burden on the SV. Supporting and maintaining the physiology of parallel systemic and pulmonary circulations with a Qp: Qs of 1.0 remain the objective throughout the post-CPB period. Postoperatively, the heart has incurred the cost of insults related to CPB, cessation of coronary perfusion, and DHCA, which may contribute to the cardiovascular frailty often exhibited in the early postoperative period. However, in the absence of major deficiencies in myocardial protection or

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persistent anatomic residua, such as significant aortic arch obstruction, coronary compromise, or valvular insufficiency, myocardial dysfunction can usually be addressed with relatively modest doses of inotropic agents and vasodilation. Low dose epinephrine (0.03–0.05 mcg/kg/min) and milrinone (0.25–0.5 mcg/kg/min) are commonly utilized after CPB. Vasopressin infusion may be added as well if necessary. While some clinicians advocate routine use of perioperative milrinone in Norwood procedures, others propose a targeted approach, citing the relatively weak inotropic and lusitropic effects of milrinone compared to its vasodilating properties. There is also conflicting evidence regarding the efficacy of perioperative milrinone in reducing mortality after the Norwood procedure [70–72]. In many neonates and young infants undergoing major cardiac interventions, myocardial performance may deteriorate in the first 6–12 hours postoperatively before it begins to improve. As a result, measures to reduce metabolic demands by providing continuous neuromuscular blockade and opioid infusions may be utilized in the immediate postoperative period. The sternum may be left open, covered by Silastic™ or other synthetic material, and stabilized with a plastic strut. This may improve hemodynamic stability as mediastinal edema is frequent in the first several postoperative days. The potentially deleterious effects of positive pressure ventilation are also mitigated. The open sternum also provides access for postoperative mediastinal exploration for bleeding, or the institution of ECMO. Sternal closure can be accomplished at the bedside 24–72 hours postoperatively.

A variety of ultrafiltration techniques, including conventional, modified, zero-balance, and combination ultrafiltration, may be utilized during and after CPB to improve postoperative hemodynamics. Several studies have demonstrated the beneficial effects of ultrafiltration upon hematocrit, hemodynamics, hemostasis, pulmonary function, and central nervous system recovery [73–78]. Perioperative weight gain is significantly reduced, as are the levels of specific inflammatory mediators. Occasionally, the position of the bypass cannulae or the continuous flux of blood through the modified ultrafiltration (MUF) circuit results in unfavorable hemodynamic changes precluding completion of the ultrafiltration. In 99 consecutive patients undergoing stage I palliation between September 2000 and August 2002, all tolerated the hemodynamic perturbations of MUF [79]. Clinical outcomes, however, have not consistently been improved and no single method of ultrafiltration has proven superior over others [73, 80]. Some institutions routinely place peritoneal dialysis (PD) catheters in the OR, and utilize PD in the early postoperative period for removal of excess interstitial fluid and potentially to remove inflammatory mediators.

Rapid restoration of normal hemostasis is an essential objective in the post-CPB period, particularly as the creation of the neo-aorta in Stage I reconstruction requires substantial arterial suture lines, and cyanotic heart disease is a predictor of postoperative blood loss [81]. Following the completion of MUF and confirmation of satisfactory technical and physiologic repair, heparin effect is reversed with protamine. Despite the theoretical advantages of fresh whole blood, studies have not demonstrated benefit from this strategy relative to the use of reconstituted whole blood [82]. Additionally, fresh whole blood is not available at most institutions. Gruenwald et al. demonstrated that a reconstituted fresh whole blood bypass prime, consisting of packed red blood cells (PRBCs), fresh frozen plasma, and platelets from the same donor, <7 days old, followed by a second such unit given after bypass, reduced bleeding in infants undergoing surgery compared with standard blood component therapy [83]. Should these measures fail to achieve adequate hemostasis despite the elimination of most surgical bleeding sites, laboratory testing (platelet count and function, fibrinogen level, and viscoelastic testing) should be conducted to direct component therapy.

Data specifically examining procoagulant medications in infants undergoing stage I reconstruction are sparse. Antifibrinolytic therapies have demonstrated efficacy in infants and children following heart surgery, but data in neonates continues to be very limited [84–87]. Although aprotinin, a serine protease inhibitor that acts as an antifibrinolytic agent with anti-inflammatory properties, demonstrated effectiveness comparable to other antifibrinolytics in infants and children [88]; this agent was voluntarily removed from the market when it was linked to greater 5-year mortality following coronary bypass grafting [89]. The lysine analogs epsilon aminocaproic acid and tranexamic acid appear to have comparable efficacy [84, 87], and extensive experience implying safety, making them appropriate substitutes for aprotinin [90].

Recombinant activated factor VII (rFVIIa) has been used as rescue therapy in infants and children following cardiac surgery, including neonates undergoing stage I reconstruction when conventional correction of postoperative coagulopathy with blood product transfusions fails to control hemorrhage [91, 92]. While rFVIIa can aid in controlling intractable bleeding, caution is warranted, as a recent retrospective review of 149 infants and children who received rFVIIa during cardiac surgery demonstrated an increased risk of thrombosis compared to control patients (20% vs. 8%) [93]. Another retrospective review of 414 neonates who underwent cardiac surgery found a 22% frequency of thrombosis in patients who received rFVIIa compared to a 6% incidence in patients who did not receive it. In neonates who underwent the Norwood procedure, those who received rFVIIa and developed thrombus had significantly higher mortality and incidence of requiring ECMO [94]. Recombinant factor VIIa may be capable of producing a hypercoagulable state that poses risks to certain surgical repair elements, including prosthetic shunts. Prothrombin complex concentrates (PCCs) may pose a similar thrombotic risk and should be used cautiously in patients undergoing stage I palliation. The 2019 patient blood management guidelines from the Network for the Advancement of Patient Blood Management, Haemostasis, and Thrombosis (NATA) for neonates and children undergoing cardiac surgery recommend against the use of PCCs in pediatric cardiac surgery except in clinical trials due to insufficient efficacy and safety data [95].

Point-of-care viscoelastic tests and transfusion algorithms are increasingly used in pediatric cardiac surgery [95–97]. Cyanotic patients, including those with HLHS, are known to have abnormal thromboelastography parameters compared to normal children, with these coagulation imbalances predisposing to both bleeding and thrombosis [96, 98]. The development of institution-specific, target-population transfusion

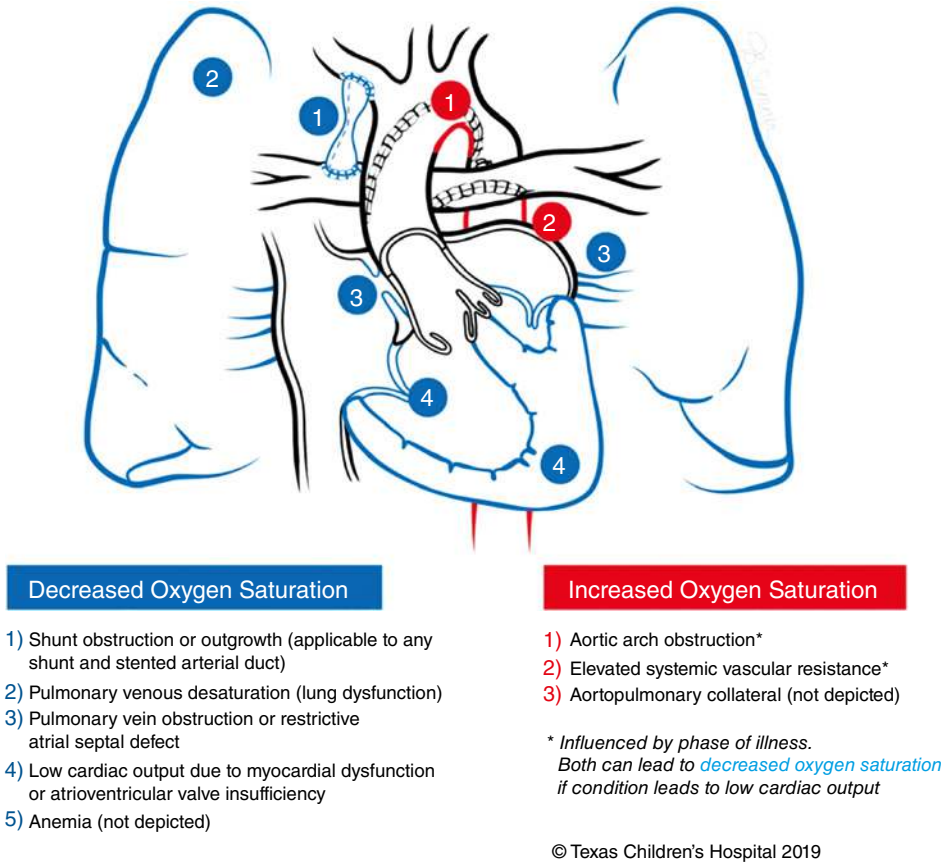


Figure 30.6 Pathophysiology associated with changes in oxygen saturation for shunt-dependent single ventricle heart defects. The figure illustrates differential diagnoses to consider when oxygen saturation thresholds are breached after Norwood palliation with a modified Blalock-Taussig shunt for hypoplastic left heart syndrome. Similar pathophysiologic considerations are applicable to the right ventricle to pulmonary artery shunt, hybrid palliation, and other shunt-dependent single ventricle variants. (Source: Rudd et al. [104]. Reproduced with permission from Texas Children's Hospital. © 2019 Texas Children's Hospital.)

algorithms may lead to reduced intraoperative transfusions and improved outcomes. However, additional data regarding patients undergoing stage I palliation is needed [96, 97, 99]. As PRBC transfusion has been associated with a longer duration of mechanical ventilation and ICU stay in stage I palliation patients [100], the Pediatric Critical Care Transfusion and Anemia Expertise Initiative released recommendations regarding red blood cell transfusion in patients with CHD. These recommendations state transfusions should be avoided "solely based upon hemoglobin, if hemoglobin is >9.0 g/dL in infants undergoing staged palliative procedures with stable hemodynamics" [101]. Further details of coagulation and bleeding management are discussed in Chapter 16.

Postoperative considerations

Excessive hypoxemia represents one of the more commonly encountered problems in the early post-CPB period. Although inadequate Qp:Qs is often the cause, factors that impair systemic oxygen delivery and reduce mixed venous oxygen saturation can also occur [63, 64, 102, 103]. A progressive increase in systemic oxygen saturation is often observed during MUF, likely due to the effect of hemoconcentration and the resulting increased oxygen delivery on mixed venous oxygen saturation. Post-CPB, measures directed at maintaining the hematocrit above 40–45% may alleviate excessive demands placed upon the recovering heart to increase systemic output. The distinction between systemic hypoxemia due to low Qp:Qs, low pulmonary venous oxygen saturation, or low mixed venous oxygen saturation (SvO_2) is crucial as the therapies for each differ. Measures designed to reduce PVR will impose a further volume load on a heart already struggling to provide marginal systemic perfusion. Patients demonstrating low SvO_2 are better served with therapies that promote systemic output, such as inotropic agents or vasodilators (see Figure 30.6) [104].

Similarly, infants with low pulmonary venous oxygen saturation require a strategy of ventilatory support designed to reduce atelectasis and promote gas exchange in impaired alveoli. Although pulmonary vein desaturation is not the most common cause of persistent systemic hypoxemia after stage I palliation, one series found pulmonary vein desaturation in as many as 30% of patients [105]. Unfortunately, this diagnosis is rarely made definitively in the OR or cardiac ICU due to the logistical challenges of blood sampling from the pulmonary veins. Intraoperatively, expectant measures

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directed at expansion of the lungs and maintenance of normal functional residual capacity (FRC) usually suffice to avoid pulmonary vein desaturation.

When systemic hypoxemia is suspected to be due to low Qp: Qs, other manifestations can provide supporting evidence. A trial opening of the systemic-to-pulmonary artery shunt during the latter phases of rewarming on CPB may have failed to demonstrate a significant drop in the mean systemic arterial pressure, and early post-CPB hemodynamics may have revealed a relatively narrow pulse pressure and/or high diastolic pressure. A substantial discrepancy may exist between arterial and end-tidal CO_2 measurements. These suggestive pieces of inferential evidence can be confirmed by aortic Doppler flow analysis or calculation of a Fick ratio using oxygen saturation determinations. Most commonly, diminished PBF may reflect a subtle technical aspect of the arch reconstruction, innominate artery dimension, or shunt placement. However, specific patient subsets can exhibit profound abnormalities in the pulmonary vasculature that result in excessive PVR elevations. Neonates born with HLHS and severe pulmonary venous obstruction due to intact atrial septum without alternative decompressing veins routinely demonstrate extremely high and volatile PVR. Even the typical HLHS anatomic constellation is associated with marked abnormalities in the number and muscularization of the pulmonary vasculature by pathologic examination. Hypotheses attribute these changes to chronic fetal pulmonary venous obstruction [106, 107]. One can speculate that these changes become more extreme in the context of the significant obstruction caused by HLHS with an intact atrial septum. Fetal echocardiography has confirmed alteration in pulmonary venous flow pattern in relation to the magnitude of restriction at the atrial septum [108].

In the context of hypoxemia due to low Qp:Qs, interventions fall into three categories: surgical modification, pulmonary vasodilation measures, and systemic vasoconstriction. In the subgroup of patients expected to have unusually elevated PVR, surgical modifications might entail placement of a larger shunt or placement of a central shunt (PTFE shunt from the aorta to the pulmonary artery). Potential pulmonary vasodilator therapies include the strategies one might employ in any patient demonstrating elevated PVR, such as supplemental oxygen, moderate hyperventilation, normothermia, alkali, and inhaled nitric oxide (iNO) [109–111]. Additionally, the use of higher doses of inotropic infusions or even vasoconstrictors to increase the driving pressure across the shunt may be considered. The latter necessitates careful monitoring to avoid jeopardizing perfusion to other vital organs.

The depressed myocardial function represents another potential problem in the early post-CPB period. Some degree of myocardial dysfunction typically occurs following stage I palliation, as no hemodynamic benefit is achieved that offsets the cost of CPB and an ischemic interval. When this dysfunction becomes more significant than usual, specific causes should be sought. Even in the context of the typical conduct of stage I reconstruction, the presence of AA can make routine myocardial protection measures, such as the infusion of cardioplegia solutions, challenging, and thus inadequate myocardial preservation represents one potential cause for persistent or excessive myocardial depression.

Technical considerations represent the predominant cause of myocardial dysfunction following this complex intervention. One of the most complex aspects of this procedure is the reconstruction of an aortic arch so that the small ascending aorta, which principally serves to provide coronary flow, is not compromised. Problems with retrograde flow to the coronary arteries may not become evident until the cardiac volume is restored in anticipation of terminating CPB. Residual hemodynamic derangement represents another potential cause of myocardial dysfunction. Given that under the best circumstances, the Norwood operation does not provide appreciable hemodynamic benefit, one would expect that a surgical result with newly imposed volume or pressure loads would be poorly tolerated. Examples of such findings include residual aortic arch obstruction, AV valve dysfunction, and/or semilunar valve obstruction or regurgitation.

Metabolic disturbances can also result in significant myocardial dysfunction. A fragile RV struggling to cope with significantly increased volume output demands at systemic pressure is perhaps more susceptible to what might otherwise be modest metabolic disturbances. As such, variables that can impact myocardial performance, such as ionized calcium levels and the presence of lactic acidosis, should be monitored closely and observed for trends. The rapid administration of blood products containing calcium-binding drugs, high levels of potassium, and lactic acid, along with other vasoactive mediators can result in an acute, profound deterioration in cardiac performance in the early postoperative period. When the arterial pH falls below 7.3, myocardial performance may deteriorate and contribute to a further reduction in Qs. The administration of IV bicarbonate, calculated to eliminate the base deficit completely, often exerts a beneficial effect on both myocardial performance and Qs. In addition to the inherent cardiac sensitivity, certain anatomic factors accentuate this vulnerability to metabolic disturbances. Blood carrying the transfused products from the systemic venous circulation enters the RV and is directed immediately to the reconstructed aorta, which has as its first branch the coronary arterial circulation. Thus, constituents of the transfused blood (e.g., citrate, potassium, lactate) infused into the venous circulation arrive at the coronary arteries with greater speed and more concentration than might have occurred had they been dissipated throughout the pulmonary vasculature before entering the aorta. This effect is further accentuated if central venous catheters are employed to infuse the blood product. It is best to utilize either washed packed cells or blood that is <7 days of age.

Arrhythmias most commonly occur as manifestations of the problems described previously. When they occur early in the rewarming process on CPB, coronary insufficiency represents the most common cause, particularly if the arrhythmia is ventricular in origin. Metabolic disturbances produce the same qualitative rhythm changes seen in normal hearts, although the manifestations might be more extreme. Given the predominantly extracardiac nature of the Norwood procedure, acquired heart block rarely follows this operation unless it existed preoperatively. On rare occasions, a patient presents with HLHS and a primary arrhythmia, such as Wolff–Parkinson–White syndrome. A 2021 retrospective review of 120 patients with HLHS after the Norwood procedure demonstrated a 26% incidence of postoperative

arrhythmias. Of these, the majority (32.4%) were ectopic atrial tachycardia [112].

Excessive PBF may complicate the early postoperative period; however, this diagnosis should be entertained cautiously. In many instances, the apparent excess PBF reflects a relative imbalance with respect to significantly diminished systemic CO (Qs). The latter should be specifically excluded and addressed before invoking extreme measures to restrict PBF. Of course, subtle technical differences in the conduct of the operation can result in an anatomic propensity to an excessive Qp: Qs, which can, in turn, jeopardize systemic perfusion. Such patients typically exhibit an extremely wide pulse pressure or low diastolic pressure, reflecting pulmonary "run-off." If myocardial performance otherwise appears robust, specific measures employed to increase PVR are appropriate in this setting. In most patients, this condition dissipates as the infant recovers from surgery. Should the problem persist beyond the first postoperative day, cardiac catheterization should be considered to evaluate the need for further surgical intervention to diminish PBF.

The subset of patients who demonstrate either an inability to separate from CPB or refractory cardiac dysfunction postoperatively may benefit from ECMO utilization as a support strategy. Ungerleider et al. have advocated the routine use of mechanical ventricular assistance in all patients following stage I reconstruction, reporting 89% survival to hospital discharge [113]. According to data from the National Pediatric Cardiology Quality Improvement Initiative database, 66 of 931 (7.1%) HLHS patients required ECMO during admission for stage I palliation. Patients requiring ECMO had a significantly higher risk of death or transplant (18%) compared to those who did not require ECMO (9%) [114]. Risk factors described for post-Norwood ECMO requirement include birth weight <2.5 kg, longer CPB time, peak serum lactate >9 mmol/L, and the vasoactive inotropic score of >27 [115]. An analysis from the Extracorporeal Life Support Organization of 738 HLHS patients requiring ECMO after stage I palliation demonstrated a 31% survival rate. Longer duration of mechanical ventilation before ECMO, longer duration of ECMO support, and ECMO complications such as renal failure or neurologic injury, all increased the risk of mortality [116, 117].

The risk of cardiac arrest in neonates with HLHS remains a concern in stage I postoperatively and the inter-stage period until SCPC is performed [118]. According to the Society of Thoracic Surgeons Congenital Heart Surgery Database, there was a 12.7% incidence of cardiac arrest among stage I palliation patients between 2007 and 2012. CPR in this population is also difficult, with a 62.3% mortality rate compared to 12.5% mortality in patients who did not experience an arrest [119]. The 2020 American Heart Association Pediatric Advanced Life Support guidelines include a specific section regarding the resuscitation of patients with SV physiology [120]. In stage I palliated patients, chest compressions provide both pulmonary and systemic blood flow, while chest recoil increases filling to the SV. Due to the parallel circulation, systemic blood flow will be lower and may have a low oxygen content, leading to coronary ischemia, systemic hypoperfusion, and end-organ damage [118]. Cardiac arrest and resuscitation are discussed in greater detail in Chapter 25.

The European Association for Cardio-Thoracic Surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC) recently developed a set of guidelines for managing neonates and infants with HLHS. These guidelines include suggested management for diagnosis, imaging, preoperative assessment, surgical and anesthetic management, and inter-stage monitoring. These recommendations allow practice standardization and identify potential targets for practice improvement at individual institutions [121]

KEY POINTS: HYPOPLASTIC LEFT HEART SYNDROME

- Preoperative stabilization of HLHS requires PGE_1 infusion to maintain ductal patency, along with measures to balance Qp: Qs near 1: 1. Room air ventilation and mild hypercarbia are often required to elevate PVR.
- Stage I palliation involves reconstruction of the hypoplastic aorta, with the pulmonary valve becoming the neo-aortic valve. Coronary perfusion is dependent on a technically sound anastomosis.
- Pulmonary blood flow is supplied by either a systemic-to-pulmonary shunt or an RV-to-pulmonary shunt; mid- and long-term outcomes are equivalent for either shunt type.
- Hybrid palliation involves a non-bypass surgery to place PA bands combined with interventional catheterization to stent the PDA and possibly the ASD; a comprehensive stage II palliation involving aortic arch reconstruction is done at the time of the SCPC.
- Interstage mortality between stage I palliation and SCPC continues to be an issue, currently at about 10–12%.

Tricuspid atresia

Incidence, anatomy, and natural history

TA is a cyanotic congenital heart defect characterized by total agenesis or complete obstruction of the AV valve associated with the morphologic RV. Tricuspid atresia accounts for approximately 1% of all cases of CHD. It is the fourth most common form of cyanotic CHD, following transposition of the great arteries, Tetralogy of Fallot, and HLHS. Its incidence, similar in males and females [122], is 1 per 10,000 individuals [123]. Tricuspid atresia occurs due to the disruption of tricuspid valvulogenesis, a multistep process, and genetic mutations in specific pathways (NFATC1 gene, Wnt/beta-catenin, RASA1, and Ras/ERK cascade) have been proposed to underlie certain cases of TA [124, 125].

Tricuspid atresia results in the absence of the RV inlet and varying deficiency of the trabecular portion of the RV, leaving the RV composed mainly of an infundibular portion and resulting in a functionally single LV (Figure 30.7) [126]. Other anatomic characteristics of TA include the presence of an interatrial defect (either ASD or PFO) and an enlarged left-sided AV valve. A ventricular septal defect (VSD) is nearly

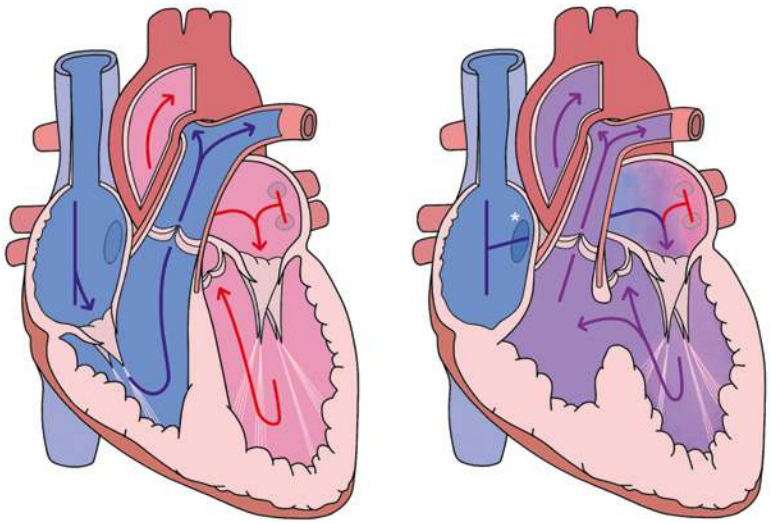


Figure 30.7 Blood flow in tricuspid atresia. (A) Normal cardiac anatomy. (B), Tricuspid atresia. *, patent foramen ovale or atrial septal defect. ASD, atrial septal defect; TA, tricuspid atresia. (Source: Sumal et al. [126] / John Wiley & Sons / CC BY 4.0.)

universally present, and abnormalities such as pulmonary stenosis (PS) may occur as well. In cases where a VSD is not present or pulmonary outflow obstruction is complete, the patient's PBF will rely on the presence of a PDA. The amount of PBF is determined by the degree of pulmonary outflow tract obstruction, the presence and size of a VSD, the relationship of the great arteries, and the presence of a PDA.

The timing and presentation of TA are determined by the degree of PBF, with approximately 50% of patients presenting on the first day of life and 80% by the age of 1 month. Without intervention, TA is associated with 90% mortality by the end of the first year of life [127]. The majority of patients present with cyanosis due to decreased PBF secondary to pulmonary obstruction and/or a small VSD. Patients with increased PBF secondary to shunting across a VSD and unobstructed PBF may initially have minimal cyanosis and progress to develop signs of excessive PBF and congestive heart failure (CHF) as the PVR falls after birth. Patients with less severe PS generally have a milder degree of cyanosis and may not require immediate surgical intervention as they have relatively balanced systemic and pulmonary circulations (see Figure 30.8) [128]. The Fontan procedure was initially applied to patients with TA, and many long-term adult survivors remain from the early Fontan era.

Pathophysiology of TA

Although different classifications have been proposed for TA, the most widely accepted schemes are based upon *the relationship of the great arteries* (Type I, II, or III) and *the degree of pulmonary outflow obstruction* (subclassification a, b, or c) (see Figure 30.9) [129]. Table 30.2 summarizes the anatomic classification, incidence, and pathophysiological features of TA.

Type I: Great artery relationships are normal. This is the most common type of TA, affecting 70–80% of patients. In the absence of a PDA, PBF is primarily dependent upon the size of the VSD and the severity of PS.

- **Type I-A**: Intact ventricular septum with pulmonary atresia (incidence approximately 10%). These patients are dependent on the presence of a PDA for PBF.
- **Type I-B**: Small VSD with PS (most common; 50% incidence). As the PDA closes, these patients will become increasingly cyanotic, related to the size of the VSD and the degree of PS. PGE_1 should be infused in these patients. The VSD may be of adequate size in early infancy, but as the heart grows and CO increases, the size of the VSD may become inadequate, resulting in increased cyanosis.
- **Type I-C**: Large VSD without PS (10% incidence). With a large VSD, PBF will depend on PVR. As PVR falls, the ratio of PBF to systemic blood flow (Qp: Qs) will increase, with hemoglobin-oxygen saturations (SaO_2) appearing near normal and pulmonary overcirculation and signs of congestive heart failure.

Type II: D-transposition of the great arteries exists. Type II affects approximately 25% of patients. Due to the transposed great arteries, the systemic outflow is dependent on the size of the VSD. Therefore, a small or restrictive VSD often results in aortic stenosis, arch hypoplasia, or coarctation of the aorta. Systemic hypoperfusion occurs as the PDA narrows and PGE_1 infusion may be necessary to maintain ductal patency. Obstruction to PBF is unusual in these patients, and they frequently develop pulmonary overcirculation and CHF in the first few weeks of life.

- **Type II-A**: A VSD exists with pulmonary atresia. In this extremely rare variant, the CO passes through the VSD into the aorta, and the patient depends on the PDA to provide PBF.
- **Type II-B**: A VSD is present with pulmonic stenosis (incidence 8%). Pulmonary blood flow is determined by the severity of PS and is often dependent on the PDA to maintain adequate oxygen saturation.
- **Type II-C**: A VSD without PS accounts for about 18% of all TA. Without PS, the relationship between PVR and any restriction to the systemic circulation (such as the size of

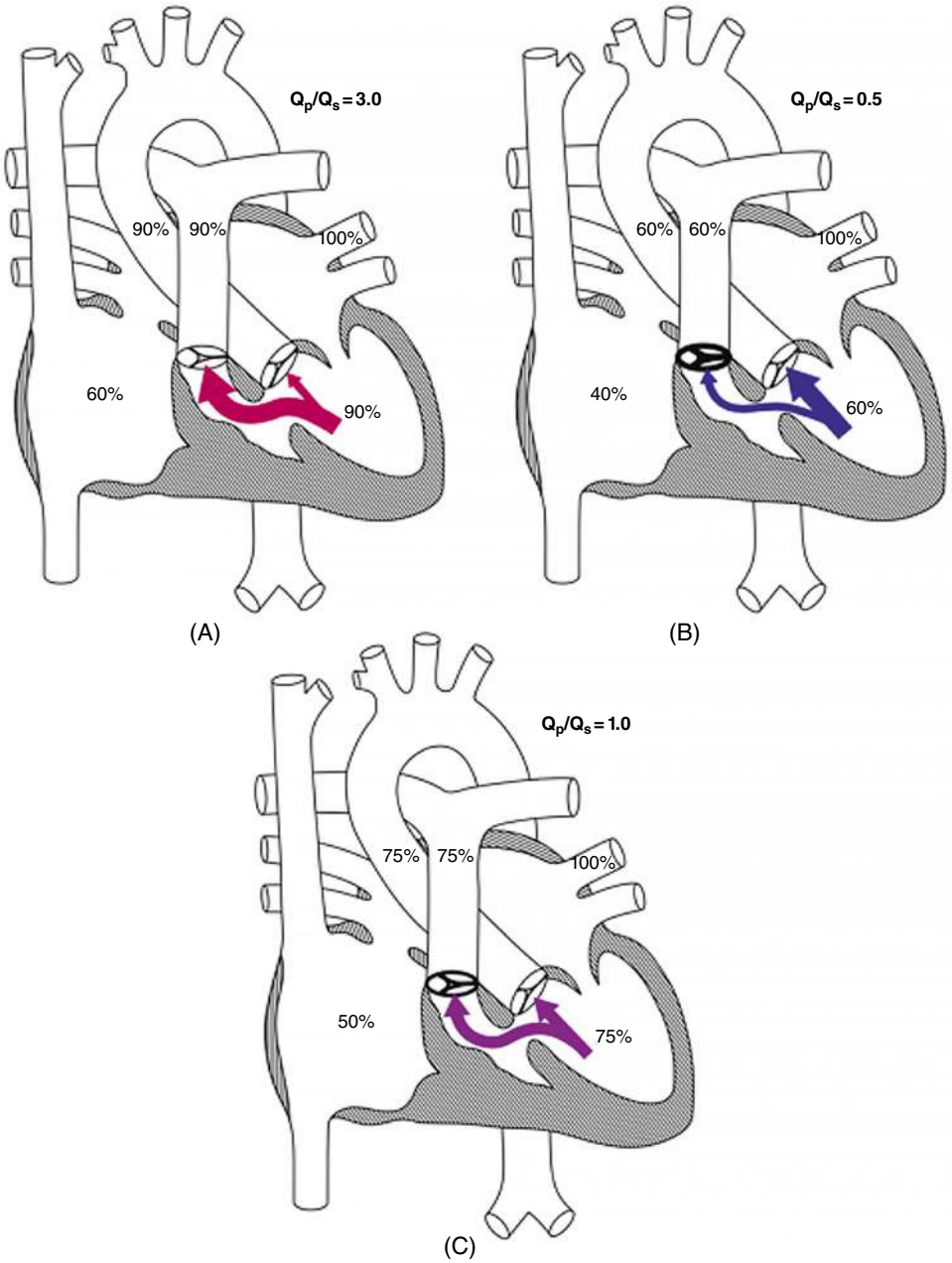


Figure 30.8 Hemodynamics of Type I tricuspid atresia with (A) no pulmonic stenosis (PS); (B) severe PS; and (C) "well-balanced" PS. Qp, pulmonary blood flow; Qs, systemic blood flow. Numbers with percentages are oxyhemoglobin saturation values. (Source: Taggart [128]. Reproduced with permission of John Wiley & Sons.)

the VSD and/or outflow tract obstruction) will determine Qp: Qs.

Type III: Malpositions of the great arteries other than d-transposition. This type is less commonly seen (3–6% of patients) and is used to classify TA with complex associated malformations such as AV septal defect or truncus arteriosus.

- Type III-A is associated with restrictive PBF due to pulmonary or subpulmonary stenosis.
- Type III-B is associated with systemic outflow obstruction due to subaortic stenosis or aortic annulus hypoplasia.

The pathophysiology of TA is determined by the degree of anatomic obstruction to PBF, the PVR, and the patency of the ductus arteriosus. The size of the VSD and the degree of PS (if present) will determine the amount of antegrade PBF that can occur left-to-right via the VSD, from the LV to the RV and the pulmonary arteries. Without communication between the RA and the RV, deoxygenated systemic venous return from the RA must travel to the LA through the ASD or PFO. Systemic arterial desaturation is present in all patients with TA due to the obligatory mixing of all venous returns (systemic, pulmonary, and coronary) in the LA. An unrestricted atrial defect is crucial to allow both venous mixing and adequate CO. If the ASD or PFO is restrictive after birth, an urgent atrial septostomy must be performed to enlarge it. Blood may also enter the PA from the aorta via the PDA.

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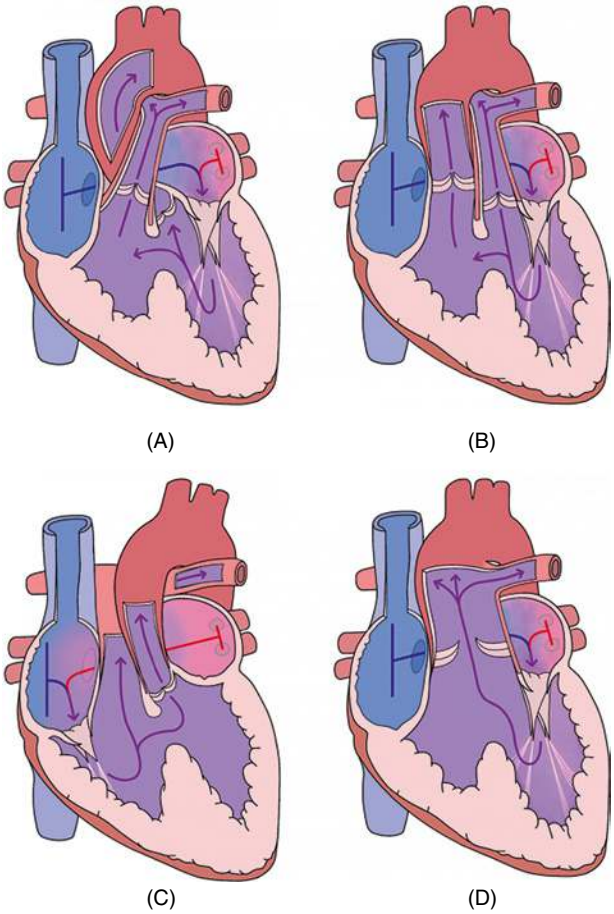


Figure 30.9 Classification of tricuspid atresia. (A) TA with normal great arteries (69%). (B) TA with D-TGA (28%). (C) TA with great-artery position other than dextro-transposition. L-TGA (subtype 1) is shown (3%). (D) TA with persistent truncus arteriosus. D-TGA, dextro-transposition of the great arteries; L-TGA, levo-transposition of the great arteries; TA, tricuspid atresia. (Source: Taggart [128]. Reproduced with permission of John Wiley & Sons.)

The diagnosis of TA is generally made prenatally with obstetrical screening ultrasound or fetal echocardiography. Postnatal diagnosis is confirmed with history and physical examination, chest radiography, electrocardiogram (ECG), and echocardiography. Chest radiography can differentiate between patients with high or low PBF as those with increased PBF demonstrate cardiomegaly and prominent pulmonary vasculature. In contrast, patients with pulmonary oligemia have a normal-sized heart and concavity in the region of the PA. The ECG demonstrates left axis deviation in the frontal plane. Echocardiography describes the anatomy and allows detailed physiological assessment and surgical planning. It aids in defining the size of the VSD and the RV, the relationship of the great vessels, degree of PS, presence and size of the PDA, and the amount of blood flow across these areas. The presence of other associated anomalies such as arch obstruction can also be assessed. Color-flow and spectral Doppler echocardiography can evaluate the adequacy of the atrial level communication (ASD or PFO). Cardiac catheterization is rarely required in the neonatal period unless necessary for balloon atrial septostomy or stenting of the PDA. Cardiac MR and CT may be used occasionally to define unusual anatomy.

Surgical and transcatheter approaches and outcomes

Ultimately TA patients will undergo staged SV palliative surgeries, culminating in the Fontan procedure. However, the necessity and type of neonatal intervention differ according to the anatomical classification and pathophysiologic consequences. The need for neonatal surgical or catheter-based intervention depends upon the degree of obstruction to PBF, the size of the VSD, and the resulting level of cyanosis. Subgroups of neonates with decreased PBF either due to pulmonary outflow obstruction and/or a restrictive VSD will require the provision of a stable source of PBF. Infants presenting with Type Ia or IIa (pulmonary atresia) are ductal-dependent until they undergo either surgical placement of a mBTTS or stenting of the PDA in the cardiac catheterization laboratory. Patients with increased PBF due to an unrestrictive VSD and either mildly obstructed (Types Ib and IIb) or unobstructed pulmonary outflow (Types Ic and IIc) often develop CHF with signs of compromised systemic perfusion. Placement of a PAB for restriction of PBF may be necessary until a superior cavopulmonary connection (SCPC) can be performed at 3–6 months of age. Infants with relatively balanced systemic and pulmonary circulations (Types Ib and IIb), although cyanotic, may not require neonatal surgical intervention and may be followed clinically for increasing cyanosis. Most often, SCPC is their first palliative surgery.

Type II TA patients with restrictive VSDs or significant subaortic obstruction require a PDA to provide systemic circulation and may undergo a "palliative" arterial switch operation (ASO) to place the aorta so that the unobstructed LV ejects into it; the VSD may need to be enlarged in this case to prevent profound cyanosis [130, 131] (See Chapter 29 for a detailed discussion of the ASO). If subaortic obstruction exists despite an unrestrictive VSD, patients may undergo a Damus–Kaye–Stansel (DKS) operation, which bypasses subaortic obstruction by creating an end-to-side anastomosis between the ascending aorta and the proximal stump of the divided PA. Either a mBTTS or RV-PA shunt is placed to provide PBF. The operative and anesthetic considerations for this surgery are similar to those for the Norwood stage I palliation of HLHS. Figure 30.10 demonstrates surgical options for TA type II with significant subaortic stenosis.

Anesthetic considerations

Pulmonary artery banding

Neonates with pulmonary overcirculation and varying degrees of CHF may present for PAB placement to protect the pulmonary vascular bed from high pressure to facilitate successful progression to SCPC and Fontan physiology. Cyanosis is mild in these patients; they are generally tachypneic and often receive diuretic therapy. Preoperative evaluation should include a thorough history and physical examination, a review of the chest radiograph for evaluation of heart size and degree of pulmonary overcirculation, and baseline pulse oximetry. A current hemoglobin level will aid in the assessment of the degree of chronic cyanosis, and serum electrolyte values can evaluate abnormalities due to chronic diuretic therapy. A review of the most recent transthoracic echocardiogram should reveal precise details of the anatomy and functional characteristics, including any mitral valve regurgitation.

Table 30.2 Anatomic and physiologic classification of tricuspid atresia

Type	Major anatomic features	Incidence	Major pathophysiologic features			Neonatal surgical approach
			Cyanosis	CHF	Decreased systemic perfusion	
Type I: Normally related great arteries		70–80%				
Ia	Intact VS with pulmonary atresia		+++	–	–	mBTS
Ib	Small VSD with PS		++	–	–	None
Ic	Large VSD, no PS		+	++	–	PA band
Type II: Transposition of the great arteries		12–25%				
IIa	VSD with PA		+++	–	Yes if VSD restrictive	mBTS
IIb	VSD with PS		++	–	Yes if VSD restrictive	None
IIc	VSD no PS		+	++	Yes if VSD restrictive	PA band
Type II: Transposition of the great arteries with restrictive VSD or subAS			++	+++	++	DKS; or subAS resection, +/– enlarge VSD; or palliative ASO, +/– enlarge VSD
Type III: Normally related or transposed great arteries with other complex cardiac lesions		3–6%	+ to +++	– to ++	Depends on associated anomalies	Depends on associated anomalies

ASO, arterial switch operation; CHF, congestive heart failure; DKS, Damus–Kaye–Stansel operation;mBTS, modified Blalock–Taussig shunt; PS, pulmonic stenosis; subAS, subaortic stenosis; VS, ventricular septum; VSD, ventricular septal defect; +, mild; ++, moderate; +++, severe; –, no effect.

Although cardiac rhythm disturbances are unusual at this stage, a 12-lead ECG is helpful to exclude arrhythmias.

After placement of standard monitors, an IV induction of anesthesia is most commonly performed, utilizing fentanyl in combination with incremental doses of either ketamine or propofol. After administration of a neuromuscular blocking agent and tracheal intubation arterial access is achieved for monitoring. Institutional viewpoints vary regarding the need and best location for placement of central venous access. Some centers advocate the use of femoral venous cannulation, due to concern for potential thrombus formation in the SVC, as it will be necessary later for successful SCPC. Others may choose to place a transthoracic RA line. If appropriate peripheral IV access exists some centers elect not to use central venous access for this procedure. The patient's preoperative condition, along with institutional preferences and the need for postoperative vascular access in the ICU, will assist in decision-making.

Steady-state anesthetic and ventilatory conditions should be maintained during the procedure in order to optimize PAB adjustments. The FiO_2 and $PaCO_2$ at the time of PAB placement should approximate baseline conditions for the patient; communication between the surgeon and anesthesiologist regarding the desired conditions is essential. A FiO_2 of 0.30 or less is generally utilized, and $PaCO_2$ is often in the mid-40s mmHg due to the metabolic alkalosis from diuretic therapy and the mild state of respiratory insufficiency from CHF. Many centers use TEE guidance during PAB placement.

The operation is usually performed through a median sternotomy without CPB. After dissection, the surgeon places a thin cotton tape or strip of Gore-Tex around the main PA, using care not to impinge on the branch PAs or pulmonary valve. A formula derived by Trusler advocated an initial band circumference of 24 mm + 1 mm/kg body weight for infants with bidirectional mixing disorders, but this was subsequently modified for patients with univentricular physiology, narrowing the circumference further to 22 mm + 1 mm/kg [132, 133]. Various methods may be used to assess and adjust PAB tightness. The primary method is to assess the change in pulse oximeter saturation and the measured arterial PaO_2 saturation after band placement, with a SpO_2 of 75–85% and a PaO_2 of approximately 40–45 mmHg customarily targeted. Transesophageal echocardiography helps measure peak velocity (V) across the PA band; 3 m/s is a frequent goal and corresponds to a pressure gradient of 36 mmHg using the modified Bernoulli principle (peak velocity = $4V^2$). Additionally, echocardiography can reassure that no encroachment on the pulmonary valve or distortion of the pulmonary arteries has occurred. Finally, direct pressure measurement in the surgical field is utilized by some institutions; a PA pressure distal to the PAB that is about one-third of systemic arterial pressure (range, 25–50%) is a frequent goal. The PAB is adjusted temporarily with surgical clips, blood gas measurements can be obtained after steady-state conditions are achieved, and the band is then permanently secured with non-absorbable sutures. An overly tight PAB will produce profound cyanosis and bradycardia, while one that is too loose will produce little change from baseline conditions. The final PAB circumference is often determined by surgical judgment, hence the importance of achieving and maintaining steady-state anesthetic and ventilatory conditions.

Although usually not necessary, inotropic support should be readily available as afterload will increase after placement

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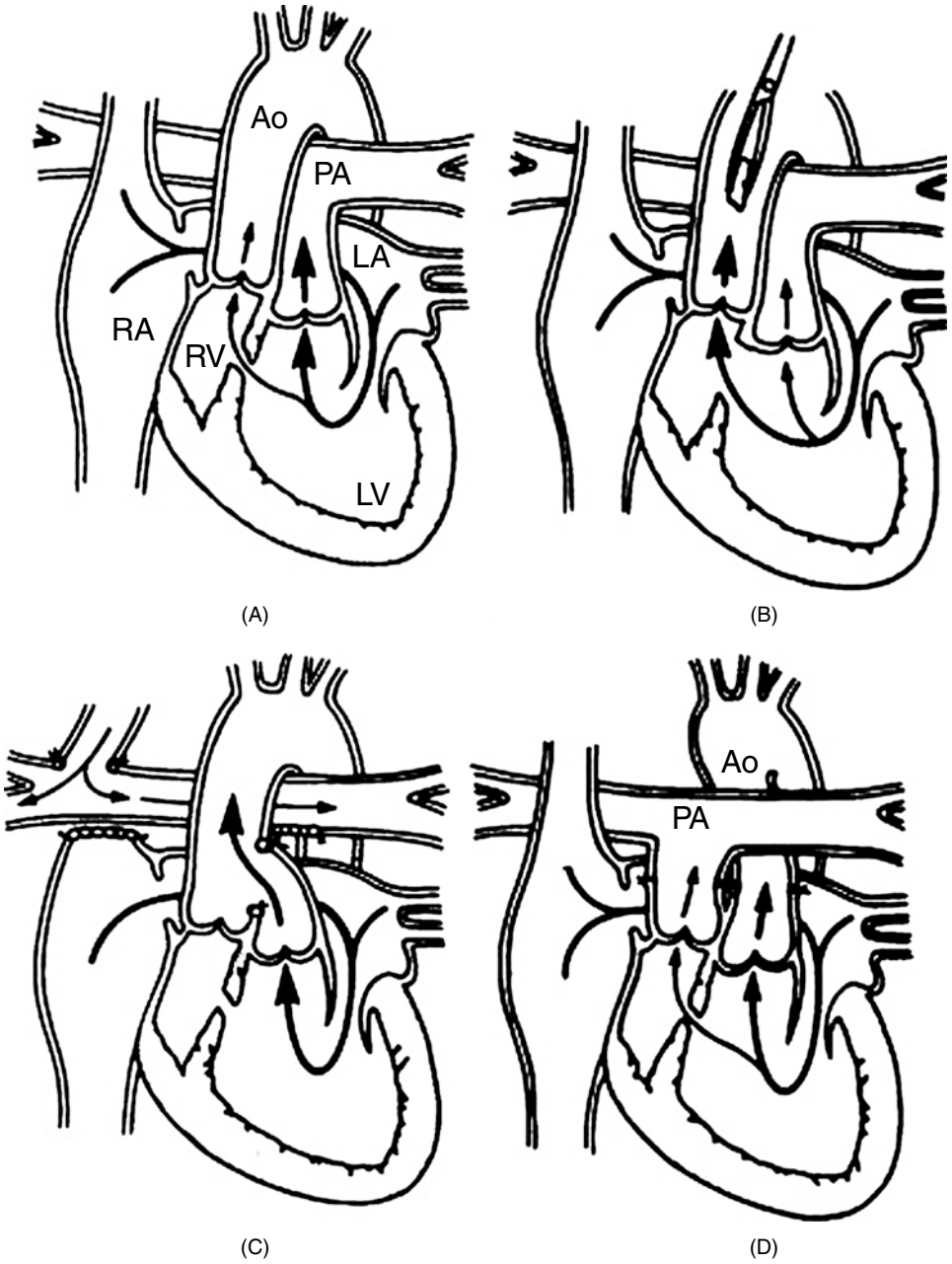


Figure 30.10 Surgical methods for tricuspid atresia type II with significant subaortic stenosis. (A) Preoperative anatomy of tricuspid atresia type IIc. (B) Direct resection of subaortic myocardium with enlargement of the ventricular septal defect. (C) Damus–Kaye–Stansel operation: main pulmonary artery to aorta end-to-side anastomosis. (D) Palliative arterial switch operation. Ao, aorta, LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

of the PAB once the pulmonary circuit no longer provides a low resistance "pop-off." Placement of a PAB mechanically increases the resistance to PA flow, and therefore, more blood flow is directed out through the aorta. Systemic arterial pressure often increases after placement of a PAB, and occasionally a vasodilator such as sodium nitroprusside is necessary to control blood pressure. After surgery, tracheal extubation may occur in the OR or within the first few hours of ICU admission.

As the patient emerges from anesthesia, CO changes, along with the relative tightness of the band. As infants are in a period of rapid somatic and cardiac growth, they often "outgrow" the PAB, and cyanosis increases. As nearly all of these infants undergo an SCPC within a few months, this issue is not usually problematic in the infant SV population.

Systemic-PA shunt and ductal stenting

Patients with TA and either pulmonary atresia or significant PS who require PGE_1 and maintenance of ductal patency for PBF may present for either surgical placement of a mBTTS or placement of a ductal stent in the cardiac catheterization

laboratory to establish a stable source of PBF. Occasionally an older infant with profound cyanosis and a closed ductus arteriosus may also present for placement of an mBTTS. Although an mBTTS can be performed via right thoracotomy, the median sternotomy approach is most commonly utilized. Unless necessary due to hemodynamic instability or significant hemoglobin-oxygen saturations during the procedure, CPB is not utilized. The anesthetic considerations for placement of an mBTTS are presented in detail in Chapter 28.

Percutaneous transcatheter stenting of the ductus arteriosus was first described in 1992 and has continued to increase in prevalence as an alternative palliative approach to secure PBF in patients with duct-dependent lesions [134]. Ductal stenting (DS) has proven to be a reasonable alternative to the mBTTS, as it is associated with similar or improved symmetrical PA growth, fewer procedural complications, a shorter ICU and hospital length of stay, and improved survival compared to surgical shunt [135, 136]. In comparing the two procedures, cardiac arrest, the need for extracorporeal circulatory support, arrhythmias requiring therapy, and bleeding were observed only in the mBTTS group, while access site injury was observed in the DS group [137]. As the experience continues to grow and early technical challenges are overcome, DS is emerging as a preferred alternative to the mBTTS. Further detail about ductal stenting is presented in Chapter 34.

Unplanned reinterventions to treat cyanosis before SCPC may be required in patients with either mBTTS or DS. These interventions most commonly involve either balloon or stent angioplasty of the PDA stent or mBTTS, or surgical revision [136]. Planned reinterventions may also occur in DS patients, with reexpansion of the stented ductus allowing adjustment of PBF over time. A study comparing pre-SCPC hemodynamics and PA growth in SV patients palliated with either DS or mBTTS found no significant differences between the two [138].

Damus-Kaye-Stansel operation and palliative ASO

Management of patients with unrestrictive PBF and systemic ventricular outflow tract obstruction (TA with associated TGA) remains challenging. Systemic blood flow must pass through the VSD, or bulboventricular foramen, to a rudimentary subaortic outlet chamber. The VSD may become restrictive, limiting blood flow, or ventricular hypertrophy after placement of a PAB may further increase outflow obstruction. While early relief of obstruction is essential, surgical management of this issue has not been uniform. Although subaortic stenosis may be relieved directly by means of VSD and/or subaortic chamber enlargement, this incurs the risks of heart block, recurrent stenosis, and ventricular dysfunction due to the ventriculotomy. As noted earlier, the DKS operation may be performed for TA variants with significant subaortic or aortic obstruction or with a restrictive VSD. The anesthetic considerations are very similar to those for Norwood stage I palliation, as discussed earlier. Because the single functional ventricle is an LV, and because the aortic valve is not atretic and the coronary artery circulation not as tenuous as in HLHS, these patients are generally expected to have a more stable pathophysiologic condition after DKS, compared with the Norwood stage I palliation. The palliative ASO has many anesthetic considerations in common with the standard ASO for d-TGA with two ventricles (discussed in Chapter 29). The major difference is that TA remains, and adequate PBF needs to be assured after the ASO, often requiring enlargement of the VSD or possibly placement of an mBTTS.

KEY POINTS: TRICUSPID ATRESIA

- TA results in a single systemic LV with a rudimentary RV.
- Type I TA has normally related great vessels, type II has d-TGA, and type III has l-TGA or additional complex cardiac defects.
- Subtype *a* has pulmonary atresia, *b* has PS, and *c* has no PS.
- Neonatal surgical palliation depends on the size of the VSD and the degree of obstruction to pulmonary or systemic blood flow. The majority of patients require the establishment of stable PBF via either mBTTS placement or DS. Patients with unrestrictive PBF often require PA banding. Complex repairs such as the DKS operation or palliative ASO can be required in patients with TA and TGA.

Other forms of univentricular hearts

In addition to HLHS and TA, other forms of univentricular hearts exist and can present in the neonatal period for initial surgical palliation [137]. These patients virtually always undergo staged palliation with SCPC at 3–6 months and Fontan completion between 18 months and 4 years of age. Although collectively accounting for only 1–2% of all CHD patients diagnosed at birth, the congenital cardiac anesthesiologist frequently encounters these patients for surgical and catheterization procedures, imaging procedures, and noncardiac surgery. Table 30.3 summarizes other univentricular heart variants.

Double inlet ventricle

In a double inlet ventricle, both atria connect only to a single ventricular chamber, either via a common AV valve or two separate AV valves. The AV valves may be normal, or one may be hypoplastic, stenotic, or atretic [137]. The additional ventricle is hypoplastic; in some cases, there can be a partial connection to the rudimentary ventricle via a straddling AV valve. In general, the rudimentary ventricle lacks an inlet portion, but the outlet chamber can also be absent. A VSD or bulboventricular foramen is usually present and may restrict flow to the outlet chamber and the attached great vessel. Although the single functional ventricle can be a morphologic LV, RV, or have indeterminate morphology, double inlet left ventricle (DILV) is the most commonly seen variant (see Figure 30.11).

A right-sided anatomic LV exists in the double-inlet left ventricle (DILV) along with frequent ventriculoarterial discordance, with l-TGA occurring slightly more frequently than d-TGA [137, 139]. The clinical picture varies according to the size of the VSD or bulboventricular foramen, the

Table 30.3 Other types of univentricular heart variants presenting for neonatal cardiac surgery

Lesion	Morphology of systemic ventricle	Associated cardiac findings	Neonatal surgical palliation options
Double inlet ventricle	Left is most common	L-transposition of the great arteries; subAS; subPS	Damus–Kaye–Stansel; palliative ASO; PA banding
Mitral atresia with VSD	Right	Restrictive bulboventricular foramen; hypoplastic aortic arch	Damus–Kaye–Stansel; PA banding
Unbalanced common AV canal	Right or left	Coarctation or arch hypoplasia	Aortic arch repair; PA banding
Heterotaxy syndrome with single ventricle	Right, left, or indeterminate	PS; bilateral SVC; interrupted IVC; TAPVR	mBTS; TAPVR repair; PA banding

AS, aortic stenosis; ASO, arterial switch operation; IVC, inferior vena cava; mBTS, modified Blalock–Taussig shunt; PA, pulmonary artery; PS, pulmonic stenosis; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return; VSD, ventricular septal defect.

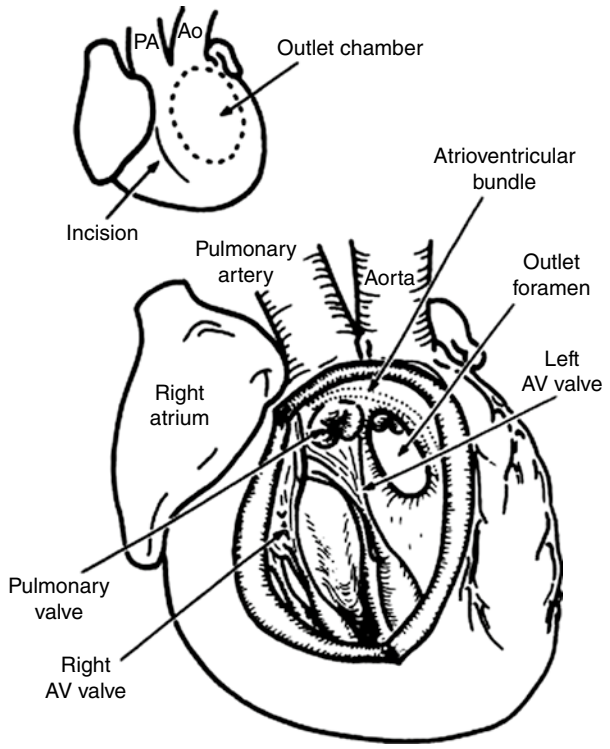


Figure 30.11 Double inlet left ventricle with hypoplastic right ventricle. Relationships of the intracardiac structures and the disposition of the conduction tissue (atrioventricular bundle). Ao, aorta; AV, atrioventricular; PA, pulmonary artery.

presence of AV valve hypoplasia or stenosis, and the morphology and degree of pulmonary or systemic outflow obstruction. Three subtypes of DILV have been described according to the relationship of the great arteries [140].

- **Type I**: Normally related great arteries are found; this anomaly is also known as the "Holmes" heart.
- **Type II**: d-TGA exists, often associated with obstruction of the bulboventricular foramen and subaortic stenosis. Aortic arch anomalies exist approximately 50% of the time as well.
- **Type III:** l-TGA is present. Subaortic obstruction occurs in two-thirds of patients due to a small bulboventricular foramen or left AV valve tissue obstruction.

The appropriate neonatal surgical palliative approach will depend on the exact anatomy and its pathophysiological consequences. Patients with restrictive PBF require a mBTTS or PDA stenting, while those with aortic valve and aortic hypoplasia may require a Norwood procedure, DKS operation, or palliative ASO (see earlier). Some centers may choose the placement of a PAB along with aortic arch repair. Patients without restriction to either pulmonary or aortic outflow usually require placement of a PAB, while in patients with a balanced circulation the initial palliative surgery is generally an SCPC. Anesthetic considerations for these procedures are discussed earlier in the chapter. Current outcomes of multistage palliation for DILV compare favorably with those reported for other SV anomalies [139].

Mitral atresia with VSD

Mitral atresia with VSD denotes the absence of the left AV valve connection from the LA to the LV, resulting in a functionally univentricular heart with a dominant RV and a hypoplastic LV connected to the RV via a VSD or bulboventricular foramen. Both the aorta and PA may arise from the RV, and the aortic root may be normal, or the aorta can arise from the small LV, in which case the aorta is often hypoplastic and classification then becomes HLHS. The majority of cases are seen in conjunction with other ventricular anomalies such as HLHS, left ventricular outflow tract obstruction, and double outlet RV. Neonatal palliation often consists of PAB placement in patients with unrestrictive flow through both great vessels; a DKS or Norwood stage I palliation operation is usually necessary if subaortic obstruction or hypoplasia of the ascending aorta also exists.

Unbalanced complete atrioventricular septal defect

Unbalanced complete atrioventricular septal defects (uCAVSDs) compose approximately 10% of CAVSDs [137]. As in balanced CAVSD (see Chapter 26), a single common AV valve exists along with a large primum ASD and a large inlet VSD. However, in uCAVSD, one ventricle is hypoplastic, often resulting in a single functional ventricle. A right dominant uCAVSD is more commonly seen, with a large RV and hypoplastic LV. Conversely, a left dominant uCAVSD has a large LV and hypoplastic RV. Abnormal development of aortic outflow, with arch hypoplasia or coarctation, may be observed in uCAVSD, but PS is unusual.

Surgical decision-making for the patient with an uCAVSD is guided by the percentage of ventricular imbalance and the adequacy of the AV valves [141]. Echocardiography plays a vital role in determining the suitability of a candidate for single vs. biventricular repair. If the LV or RV apex is present ("apex-forming") in an otherwise small ventricle, a patient may be considered for biventricular repair. Echocardiographic measurement of the AV valve index, the ratio of the smaller AV valve component over the larger component, can offer guidance [142]. Cardiac MR imaging can yield information regarding ventricular volumes to further assist decision-making [143].

Unbalanced CAVSD patients often present in early infancy with pulmonary overcirculation. They may require placement of a PAB, either as part of a staged univentricular palliation or to allow delayed decision-making regarding the feasibility of biventricular repair. Infants with abnormalities of aortic outflow may require coarctation repair or aortic arch repair, with a PAB frequently necessary as well. As in other SV anomalies, the SCPC is performed at 3–6 months. Patients with uCAVSDs who undergo SV palliation represent a challenging group of patients, with substantial early mortality and <60% survival at 20 years [144]. In particular, trisomy 21 patients with severe ventricular hypoplasia are reported to have poor outcomes, regardless of their dominant ventricle [141].

Single functional ventricle with heterotaxy syndrome

The International Society for Nomenclature of Pediatric and Congenital Heart Disease defines heterotaxy as "an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body." Heterotaxy does not include patients with situs inversus or complete mirror imaging of cardiac and abdominal organs around the right-left axis [145]. Chapters 6 and 7 have an extensive discussion of the embryology and nomenclature of heterotaxy syndrome. Constellations of cardiac manifestations are frequently seen in patients with heterotaxy syndrome, with many requiring SV palliation. In addition to cardiac anomalies, malrotation of the intestines may be present, predisposing the patient to intestinal volvulus, and therefore, all babies with heterotaxy should be evaluated to rule out intestinal malrotation. Patients often have impaired or absent splenic function, even in the presence of polysplenia. Functionally asplenic patients are susceptible to pneumococcal and other bacterial sepsis and require lifelong penicillin prophylaxis.

Isomerism reflects the duplication of one vertical half of the body in regard to the thoracic organs, with unusual arrangements of the abdominal organs (visceral heterotaxy). Atrial appendage morphology should be the basis for segregating right and left isomerism; if morphology cannot be assigned to either right or left atrium, isomerism may be considered indeterminate. Classification is essential because right and left isomerism are associated with markedly different anatomical findings of the affected organs that can be clinically significant. Isomerism can significantly impact surgical outcomes for SV palliative surgeries, and mortality before stage I palliation and during the stage I to stage II interstage period is greater in patients with isomerism [146].

Right atrial isomerism (RAI) is associated with bilateral morphologically right atrial appendages, bilateral trilobed lungs, central nervous system anomalies, and asplenia. Associated cardiac abnormalities may include a constellation of many or all of the following: AVSD, total anomalous pulmonary venous connection (TAPVC), TGA, and bilateral SVCs. The presence of extracardiac TAPVC in a patient with heterotaxy is highly correlated with RAI [147]. Patients with RAI generally have bilateral sinus nodes, leading to a propensity for atrial arrhythmias later in life. The absence of the coronary sinus is a near-universal finding in patients with isomeric right atrial appendages [148].

Left atrial isomerism (LAI) is associated with bilateral morphologic LA appendages, bilaterally bilobed lungs, and asplenia or polysplenia. Cardiac anomalies can include all or some of the following: AVSD, partial anomalous pulmonary venous connection (PAPVC), interruption of the IVC, absence of the coronary sinus, mirror-imaged spiraling of great arteries, and AV block. Interruption of the IVC in the presence of heterotaxy is highly correlated with LAI compared to RAI. An interrupted IVC can drain into either the azygos or hemiazygos vein and from there into a right or left-sided SVC. In addition, the IVC may be left-sided and drain into a common atrium separately from the hepatic veins, presenting complexities at the time of Fontan completion. The sinus node may be abnormally located or absent in LAI, making these patients more susceptible to arrhythmias and complete heart block (see Figure 30.12) [149].

Because of the anatomical variation possible in heterotaxy syndrome, neonatal surgical palliation varies widely. Given the frequent abnormalities of systemic and pulmonary venous drainage, echocardiography alone may not sufficiently define the anatomy. Cardiac MRI, CT, or catheterization is frequently useful in this population. Because TAPVC is common, surgical repair of this condition is often the initial operation. Pulmonary valve stenosis or atresia occurs in approximately 50% of patients with RAI and <10% of those with LAI and may necessitate placement of an mBTTS or PDA stent [150]. Conversely, PAB placement may be required for patients with pulmonary overcirculation. The management of TAPVC is discussed in Chapter 26. Precise details of the patient's anatomy are essential to understand the planned surgical approach and to guide decision-making regarding the placement of invasive arterial and central venous access catheters. The presence or absence of a spleen and intestinal malrotation can be determined by abdominal ultrasound; nuclear medicine scan (hepatobiliary iminodiacetic acid [HIDA]) is used in cases where the splenic anatomy is not clear. After initial neonatal surgical palliation, approximately 85% of heterotaxy syndrome patients undergo staged palliation to a Fontan circulation. Table 30.4 summarizes the findings in heterotaxy syndrome.

Heterotaxy syndrome presents a number of challenges for perioperative teams. Despite improving statistics, hospital mortality remains consistently higher in patients with heterotaxy [151]. Within heterotaxy syndrome, survival is consistently higher for patients with LAI compared to RAI [147, 152]. Patients with RAI are nearly five times as likely to have TAPVC compared to patients with LAI, and approximately two thirds of patients with RAI have SV physiology as well. These patients

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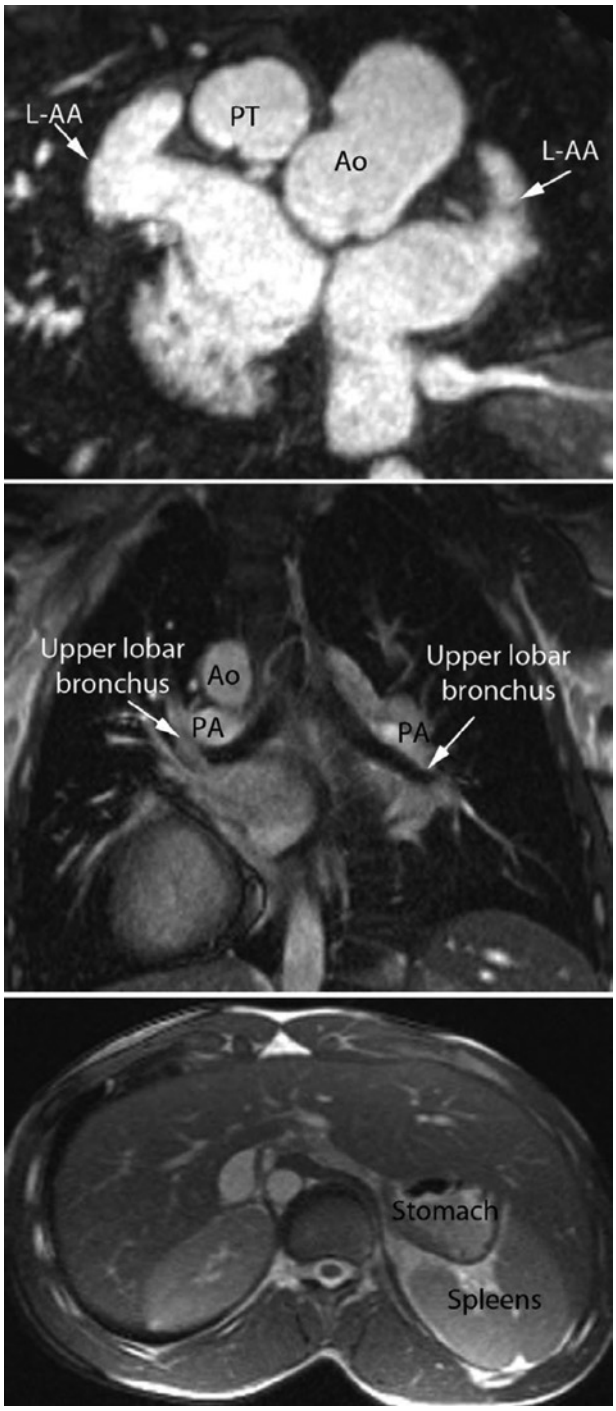


Figure 30.12 Heterotaxy with classic left isomerism and polysplenia. Both side atrial appendages are long and narrow. No pectinate muscles are seen along the wall of either atrium. The main bronchi are symmetrically long. Note the epibronchial pulmonary arteries (PA) and the hyparterial upper lobar bronchi. Two spleens are seen along the posterolateral wall of the stomach. Ao indicates aorta; DsAo, descending aorta; IVC, inferior vena cava; and PT, pulmonary trunk. (Source: Yim et al. [149]. Reproduced with permission of Wolters Kluwer Health, Inc.)

are a particularly high-risk neonatal surgical population, with 10-year survival nearly twice as high in patients without TAPVC compared to those with TAPVC [147].

KEY POINTS: OTHER UNIVENTRICULAR HEARTS

- Other univentricular hearts include double inlet ventricle, MA, unbalanced CAVSD, and various forms of SV anatomy with heterotaxy syndrome.
- Neonatal palliation depends on the degree of obstruction to pulmonary or systemic blood flow and may involve no surgery, PAB placement, systemic-to-pulmonary artery shunt, or complex repairs such as the DKS procedure or palliative ASO.
- Heterotaxy is a complex malformation syndrome involving abnormal sidedness of thoraco-abdominal organs, with isomerism classified according to atrial anatomy (right, left, or indeterminate).
- Abnormalities of systemic and pulmonary venous return are common in heterotaxy and often need to be addressed during neonatal palliation.

Superior cavopulmonary connection

Surgical procedure

The term "superior cavopulmonary connection" describes the creation of a surgical anastomosis between the SVC and the pulmonary arterial bed. If an mBTTS or RV-PA shunt is present, it is taken down at the time of SCPC; similarly, for a stented PDA, the stent(s) and PDA are excised and the aortic and pulmonary insertion sites oversewn. For patients with shunt-dependent PBF, conversion to an SCPC means that the heart is no longer required to eject systemic output plus additional output to provide PBF via the shunt. Conversion to SCPC increases effective PBF, resulting in improved systemic arterial oxygen saturation. Volume unloading of the SV also occurs, facilitating subsequent remodeling of ventricular geometry with a reduction in end-diastolic volume before Fontan completion [153, 154]. Although SCPC is the second stage in the palliative surgical sequence for most SV patients, for patients with balanced circulations who did not require a neonatal intervention the SCPC will be their first palliative surgery.

Two primary surgical options currently exist for SCPC. As outcomes appear equivalent, preference for one technique over the other tends to be institution specific. The bidirectional Glenn (BDG) is an end-to-side anastomosis of the SVC to the PA, along with ligation of the prior mBTTS or Sano shunt. A modification of the original Glenn shunt facilitated SVC flow to both left and right PAs, hence the term "bidirectional" Glenn shunt [155, 156] (see Figure 30.13). Most commonly, the BDG is followed by an extracardiac Fontan. The hemi-Fontan (HF) procedure is technically more complex and maintains the native connection between the SVC and RA; it also enables PA augmentation. The SVC-RA confluence is anastomosed to the branch PA, utilizing a "dam" within the RA to redirect SVC blood flow to the pulmonary arteries. The HF facilitates a subsequent lateral tunnel Fontan completion (see Figure 30.14). In a study utilizing multi-scale computational modeling, no significant differences in hemodynamic or physiological outcomes were seen between the HF and

Table 30.4 Findings in heterotaxy syndrome with single ventricle

Syndrome	% with single ventricle	Common cardiac variants	Pulmonary stenosis/atresia	SVC/IVC	TAPVR	SA nodes	Atrial morphology	Lung morphology
Asplenia	>50%	Single RV common; DORV, unbalanced CAVC	Common (>90%)	Bilateral SVC common	Common; to extracardiac vein	Bilateral	RA isomerism	Bilateral trilobed (right)
Polysplenia	<50%	RV or indeterminate morphology	Less common (<50%)	Interrupted IVC (80%)	To right atrium	Hypoplastic or absent	LA isomerism	Bilateral bilobed (left)

CAVC, complete atrioventricular canal; DORV, double outlet right ventricle; IVC, inferior vena cava; LA, left atrium; RA, right atrium; RV, right ventricle; SA, sinoatrial; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return.

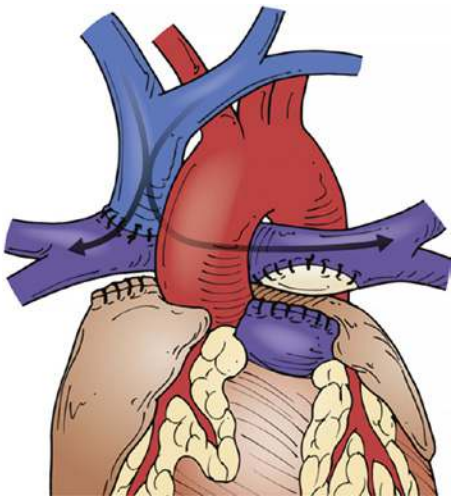


Figure 30.13 Bidirectional Glenn procedure. The superior vena cava (SVC) is anastomosed in an end-to-side fashion to the pulmonary artery. It is important to ligate the azygous vein (to limit decompression of SVC blood via the azygous to the intact inferior vena cava (IVC) circulation). The atrial junction from the SVC site is oversewn. When performed on CPB, it is often possible to complete an atrial septectomy through the atrial junction before oversewing it. Cannulation of the SVC must be performed meticulously to prevent stenosis to the Glenn circuit after the cannula is removed at the completion of the case. (Source: Murthy et al. [127]. Reproduced with permission of Elsevier.)

BDG models, suggesting that patient-specific physiology and condition are more important in determining the outcome [157]. Evaluation of infants in the SVRT dataset was done through 1 year of age, based on the type of SCPC performed. Although CPB times were longer and the use of DHCA more frequent in the HF group, no difference in transplant-free survival at 1 year was observed between groups [158].

Although SCPC may occasionally be performed as early as 2 months of age, most patients undergo this procedure at 3–6 months to allow sufficient time for PVR to decrease and permit sufficient PBF, systemic oxygenation, and systemic CO with the SCPC circulation. Consideration may be given to proceeding earlier with SCPC if increasing cyanosis from mBTTS or RV-PA shunt narrowing is present or if an urgent need exists to address other surgical issues such as coarctation of the aorta. The development of interstage home monitoring programs has dramatically improved interstage mortality for patients after Stage I palliation and assisted in planning appropriate timing of the Stage II procedure [104]. Patients with bilateral SVCs often undergo a bilateral SCPC with each SVC anastomosed to its ipsilateral PA. In this case, each SVC is generally smaller than a normal single SVC, producing increased resistance to flow. Patients requiring bilateral SCPC before 120 days of life have poorer outcomes for the Stage II procedure, but subsequently, results are equivalent for patients with either single or bilateral SVCs [159].

The HF is performed utilizing CPB. The BDG is performed with CPB support in most institutions; however, if other cardiac surgical procedures are not required, it is possible to perform an isolated SCPC without CPB with the aid of a temporary shunt from the SVC to the RA and partial heparinization. This technique is designed to prevent cerebrovenous hypertension and hypoxic-ischemic brain injury during the period of SVC occlusion. The surgical technique for isolated BDG involves the institution of CPB with cannulae in the aorta, high SVC, and RA. Cross-clamping of the aorta is avoided unless additional intracardiac procedures are planned, and mild hypothermia (32–34 °C) is generally utilized. The mBTTS or RV–PA shunt, if present, is occluded immediately after the institution of CPB and then divided and oversewn. The SVC is transected at its junction with the RA, taking care not to injure the SA node. The RA is then oversewn and the SVC anastomosed to the right PA. If pulmonary atresia does not already exist (either congenitally or as a result of incorporating the native pulmonary valve into the neo-aorta during Norwood stage I palliation), the main PA is oversewn. The pulmonary valve leaflets are also sewn closed to prevent thrombus formation in the pulmonary valve sinuses, which can embolize retrograde into the single systemic ventricle. The term "pulsatile" BDG refers to intentionally leaving some ejection from the pulmonary ventricle directly to the PA in addition to the SCPC. This elevates PA pressure and produces a pulse pressure. Reasons for utilizing this configuration can include tricuspid stenosis or other forms of mild RV hypoplasia in which the RV is deemed inadequate to receive the sum of all SVC and IVC flow. This operation is also termed a one-and-a-half-ventricle repair. Although maintaining antegrade PBF at the time of SCPC can be beneficial for oxygen saturations and the growth of pulmonary vasculature before the Fontan procedure, it has been shown to be unfavorable for overall transplant-free survival, with a higher risk of death or transplant until the antegrade flow is eliminated. [160].

Single-ventricle patients with heterotaxy syndrome (see earlier) often have bilateral SVCs, requiring bilateral SCPC.

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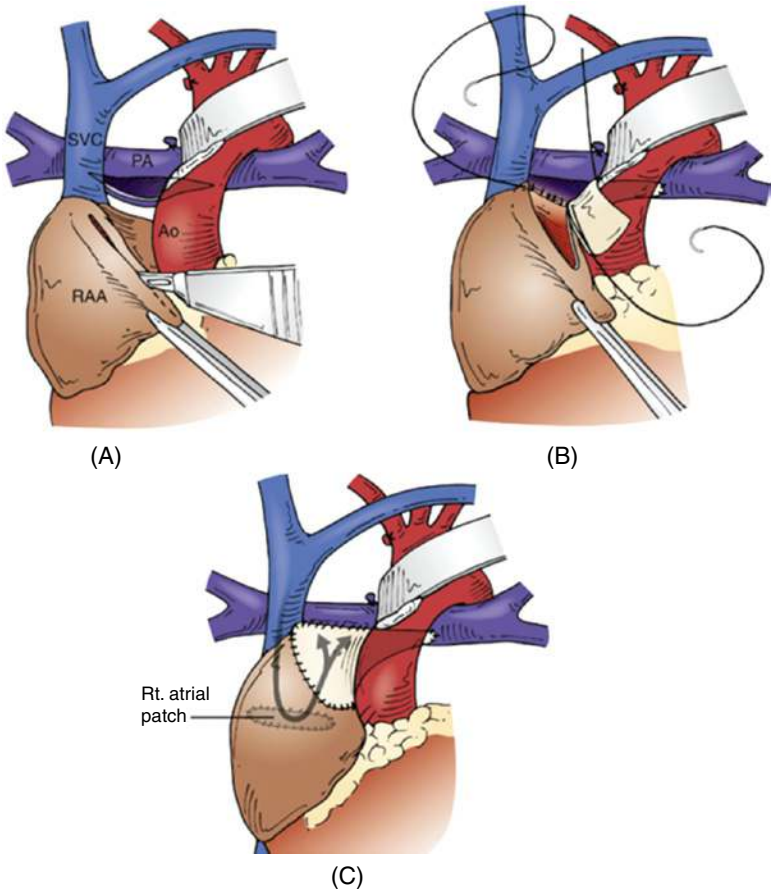


Figure 30.14 Hemi-Fontan procedure. (A) Central pulmonary arteries (PAs) are opened anteriorly from posterior to the superior vena cava (SVC) to distal to insertion of the ligamentum arteriosum. An incision is made in the base of the right atrial appendage extending up to the SVC/right atrium (RA) junction. (B) The inferior aspect of the pulmonary arteriotomy is sutured to the outside of the SVC. (C) A patch of polytetrafluoroethylene (PTFE) is sutured within the RA at the level of the limbus. (Source: Murthy et al. [127]. Reproduced with permission of Elsevier.)

These patients may also require either revision or primary repair of anomalous pulmonary venous drainage at the time SCPC is performed. Many heterotaxy patients with LAI also have interruption of the IVC. In these patients, the suprahepatic IVC is not present. Subdiaphragmatic systemic blood return occurs via collateral circulation reconstituted above the diaphragm, ultimately entering the azygous or hemiazygous circulation. Consequently, after SCPC, 75–85% of the total systemic blood flow is directed to the PAs, excluding only hepatic venous and coronary sinus drainage. The resulting physiology thus more closely approximates that seen after the Fontan operation. This operation is known as the Kawashima procedure [161]. A Fontan-type intervention is still generally performed later to incorporate hepatic venous blood into the pulmonary circulation, as these patients are at increased risk for the early development of pulmonary arteriovenous malformations (PAVMs) with resultant cyanosis due to the lack of an uncharacterized "hepatic factor" directly perfusing the pulmonary circulation. Despite this, PAVM regression remains unpredictable in these patients [162, 163].

Additional surgical procedures are frequently necessary at the time of SCPC. These can include patch augmentation of the PAs, atrial septectomy, correction of residual coarctation after Norwood stage I palliation, annuloplasty for AVVR, or correction of other significant anatomic problems. For patients who have undergone a hybrid Stage I procedure, the comprehensive Stage II procedure will involve a Norwood-type arch reconstruction, PAB removal, atrial septectomy, and removal of the DS in addition to SCPC [41, 164]. A thorough understanding of additional surgical procedures and preoperative discussion of the intraoperative plan with the surgeon and perfusionist are essential to ensure optimal patient outcomes.

Anesthetic considerations

Preoperative considerations

A successful conversion from a "parallel" circulation based upon complete mixing and parallel perfusion of both the systemic and pulmonary vascular beds via an arterial shunt to a "series" circulation where PBF becomes a diversion of systemic venous return requires certain preconditions. Preoperative evaluation should assure adequate candidacy for the SCPC, evaluating PA pressures, the size of the branch PAs, and any other anatomic issues requiring surgical intervention. As blood flow through the pulmonary circulation will be passive and dependent on the TPG after SCPC, pulmonary venous obstruction or elevations in either PA pressures

Table 30.5 Optimal pre-superior cavopulmonary connection characteristics

Age 4–6 months
Normal weight for age
Normal caloric goals during the inter-stage period
Competent systemic atrioventricular valve
Pulmonary vascular resistance <2 U/m^2
Mean pulmonary artery pressure </ = 18 mmHg
Normal ventricular function
Transpulmonary gradient <9 mmHg
No pulmonary disease leading to pulmonary venous desaturation
No venovenous collaterals
No aortic arch narrowing or re-coarctation
No pulmonary artery distortion
Single-ventricle end-diastolic pressure <12 mmHg

Source: Roeleveld et al. [28]. Reproduced with permission of Cambridge University Press.

or PVR will not be well tolerated. Optimal pre-SCPC characteristics are listed in Table 30.5 (See Table 30.5) [28].

Cardiac catheterization remains the standard imaging modality for assessing vascular anatomy before SCPC; it also provides the opportunity to measure PA pressures and resistances and perform interventions if necessary. Noninvasive methods of assessing the anatomy and physiology, such as cardiac MRI or cardiac CT angiography, have also been successfully utilized in patients who do not require catheter-based interventions before surgery [165]. Knowledge of PVR, ventricular end-diastolic pressure, AV valve function, and any residual obstruction at the atrial septum remnant is desirable before surgical intervention. Elevated PVR can encompass two distinct mechanisms: the size of the major branches and the state of the arteriolar resistance vessels. Patients who have undergone a hybrid procedure are more likely to develop PA stenosis requiring intervention. In contrast, infants who underwent conventional Stage I palliation are at a higher risk for aortic arch narrowing or re-coarctation [166, 167]. In addition, angiography can evaluate for the presence of accessory venous communications between the superior venous drainage and the heart or IVC (e.g., left SVC to coronary sinus). Postoperatively, such vessels can serve as a mechanism by which upper body venous return is diverted to the heart without passing through the pulmonary circulation, resulting in increased levels of hypoxemia. Pulmonary vein desaturation noted preoperatively may result from lung disease and later help explain low postoperative oxygen saturation.

In addition to catheterization or other imaging data, a recent ECG and echocardiogram should also be reviewed. An evaluation of other vital organ systems with a history of primary or secondary dysfunction should be incorporated, along with a detailed history regarding the child's response to sedative medications and anesthetics. For patients receiving anticoagulant medications or functional platelet inhibitors, plans for perioperative management of those therapies should be formalized. Often patients are taking low-dose aspirin with the goal of inhibiting platelet function to maintain mBTTS patency; some institutions routinely discontinue aspirin 7–10 days preoperatively, while others do not. Risk factors that have been identified for postoperative complications after SCPC include lower weight for age, female sex, and aortic atresia with mitral stenosis [168].

Intraoperative considerations

When infants return for SCPC, some may manifest early signs of separation anxiety. Although the use of sedative premedication such as oral midazolam may be considered before separation from the parents, some institutions prefer not to premedicate these patients. After placement of standard non-invasive monitoring, anesthesia can be induced with a variety of IV or inhaled agents unless preoperative assessment demonstrated ventricular dysfunction or other anatomic concerns. Although these infants have the same anatomy and physiology as neonates following Stage I palliation, maturation and compensatory mechanisms in myocardial development make them significantly more resilient. As baseline PVR is low, even extreme measures cannot produce a substantial reduction in PVR from baseline values, and therefore changes in Qp: Qs are relatively small.

Following induction and tracheal intubation, direct arterial monitoring access is obtained. The site chosen for arterial access may vary according to several considerations. The placement of an mBTTS may have compromised the ipsilateral subclavian artery, and, additionally, previous monitoring and catheterization sites may not be available. A variety of aortic arch branching patterns also exist, which can result in subclavian artery stenosis. Non-invasive arterial pressure measurement on all four extremities can aid in providing information to identify the most appropriate site(s). Institutional preferences vary regarding cannulation of the central veins, with some institutions avoiding accessing the internal jugular (IJ) or subclavian veins due to concern for thrombosis. Others may choose to cannulate the femoral vein as the major central venous access, also placing a small (3 French) catheter in the right IJ vein to monitor PA pressure for 12–24 hours postoperatively. If the IJ vein is utilized, it is essential to note catheter length and placement, as surgical cannulation occurs high on the SVC for this procedure. In addition, many centers use NIRS monitoring intra- and postoperatively, measuring both cerebral and somatic saturations.

The majority of SCPC patients are undergoing repeat sternotomy and may have mediastinal adhesions, incurring an increased risk for bleeding and pre-CPB arrhythmias from the extensive electrocautery required at times. Appropriate precautions include administration of antifibrinolytic agents, large-bore IV access with blood products prepared for immediate administration, the application of external cardioversion/defibrillation pads to the patient, and preparation of the heparin dose and a primed CPB circuit.

Unlike stage I palliation, the SCPC provides significant hemodynamic benefit. As the circulations are no longer connected in parallel postoperatively, the volume output demand for the SV is now reduced to that necessary to perfuse the systemic circulation alone. Pulmonary blood flow becomes a diversion for venous return from the upper body, effecting a "series" circulation of a pump and two resistors. As the volume of blood flow to the upper body is at least as great as that to the lower body at 6 months of age, the mixture of oxygenated and deoxygenated blood remains 1: 1 or

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higher. Thus, although the expected systemic oxygen saturation does not change appreciably, the heart is only required to perform half the volume work (Qs) to accomplish this. Although most patients exhibit robust hemodynamics on completion of this procedure, the ready availability of inotropes including epinephrine and inodilators such as milrinone is recommended, as infants with diastolic dysfunction or valvular regurgitation may benefit from them.

With PBF now reliant upon passive venous flow from the SVC, measures designed to minimize the impediments to PBF assume paramount importance. As medical therapies are limited in their capacity to produce reliable, substantial improvement in ventricular compliance or AV valve function, attention is focused on minimizing PVR. Shortly before the termination of CPB, the tracheal tube should be cleared of secretions and the lungs completely re-expanded, as PVR will be minimized at normal FRC and both atelectasis and alveolar overdistension increase PVR. A tidal volume designed to achieve a normal $PaCO_2$ at a respiratory rate no greater than 20 should be selected. Doppler flow studies have demonstrated that PBF occurs preferentially during the expiratory phase of positive pressure ventilation (PPV) in patients following cavopulmonary anastomosis and thus attempts to limit the respiratory rate and inspiratory time to <1 second are warranted [169]. Positive end-expiratory pressure (PEEP) is applied judiciously to preserve normal FRC. Ventilatory strategies producing a $PaCO_2$ of 45–50 mmHg will increase cerebral blood flow (CBF), increasing PBF through the direct SVC–PA connection. This strategy not only increases systemic and cerebral oxygen saturations but also facilitates increases in systemic oxygen delivery [170]. In instances where significant hypoxemia persists despite optimization of other measures, iNO can be used to lower PVR.

Modified ultrafiltration (MUF) offers significant benefits to patients following SCPC and is utilized immediately following the termination of CPB [171]. Postoperative blood loss and the proportion of patients demonstrating significant pleural and pericardial effusions are significantly reduced. Other investigators have shown benefits in pulmonary function that may prove particularly crucial in this population. Infants for SCPC represent a high-risk group for postoperative bleeding as they have multiple risk factors that can exacerbate bleeding, including age <2 years, reoperation, hypoxemia, frequent use of aspirin, and, for some, the use of deep hypothermic bypass management. Upon completion of MUF, the heparin effect is reversed with protamine. After acceptable hemodynamics and hemostasis are achieved, most patients can be extubated in the OR or shortly after arrival in the ICU.

Postoperative considerations

Cardiopulmonary interactions assume great importance after SCPC. Maintaining a low trans-pulmonary gradient (TPG) is essential to encourage PBF and optimize CO. Early extubation, whenever possible, facilitates this goal as PPV has been shown to reduce PBF in patients after SCPC or Fontan palliation [172]. Cerebral NIRS and cardiac index have been shown to increase while CVP decreases after extubation, suggesting that improvements in cerebral perfusion pressure (CPP) occur [173].

Systemic oxygen saturation of 75–80% is typically expected after SCPC. The presence of an SVC catheter measuring PA pressure used in combination with atrial pressure measurement yields important information. A CVP of 12–18 is often observed post-SCPC, and normovolemia should be maintained. Most institutions prefer hemoglobin levels to be maintained >13 to maximize oxygen-carrying capacity. Flow from the SVC to the pulmonary vascular bed provides approximately one-third of CO, while flow from the IVC to the atrium provides two-thirds. Assuming an oxygen saturation of 100% from the pulmonary veins and a SvO_2 of 70% from the IVC, an approximate systemic saturation of 80% can be anticipated (100 + 70 + 70/3). Decreases in PBF may therefore not affect systemic oxygen saturation as much as decreases in systemic blood flow. As multiple factors affect systemic saturations, all possible etiologies should be considered when postoperative hypoxemia of greater magnitude than anticipated persists (see Table 30.6) [174].

Low CO should be recognized promptly, as resultant decreases in SvO_2 will adversely impact systemic oxygenation and increases in ventilation will not address this issue. Instead, the goal should be to increase CO and raise IVC saturations to 70%. Although the incidence of myocardial dysfunction is low following SCPC, it does occur. In the absence of significant hemodynamic causes (e.g., aortic arch obstruction or AVVR), an issue with myocardial protection or coronary perfusion might be suspected. Despite their young age, some infants have developed extremely thick ventricular walls, particularly in the context of a high Qp:Qs and residual aortic arch obstruction. Even under optimal conditions, the compliance of these hearts may not return quickly.

Table 30.6 Potential causes of early cyanosis postbidirectional Glenn/Hemi-Fontan procedure

Pulmonary venous desaturation
Lung disease (V/Q mismatch)
Systemic venous desaturation
Low-cardiac output
Anemia
Right-to-left shunts
Venovenous collaterals (i.e., SVC to pulmonary veins or SVC to IVC)
Failure to ligate azygous or hemiazygous veins
Undiagnosed contralateral SVC (usually LSVC)
Hemi-Fontan baffle leaks (unique to HFP)
Decreased pulmonary/cerebral blood flow
ASD restriction
PA stenosis
PA thrombosis
SVC stenosis
SVC thrombosis
Elevated pulmonary vascular resistance
Elevated systemic ventricular EDP
Increased PA pressures due to additional sources of pulmonary flow
Increased intrathoracic pressure

Abbrevations: ASD, atrial septal defect, EDP, end-diastolic pressure; HFP, hemi-Fontan procedure; IVC, inferior vena cava; LSVC, left superior vena cava; PA, pulmonary artery; SVC, superior vena cava; V/Q, ventilation/perfusion.
Source: Zampi et al. [174]. Reproduced with permission of SAGE Publications.

Potential factors affecting pulmonary venous return and its impact on oxygen saturations should be considered. Pulmonary venous return can be diminished in the setting of diastolic dysfunction, AV valve insufficiency, loss of AV synchrony, or a restrictive atrial septum. Obstruction or thrombosis within the SCPC can exist; an increase in CVP aids in recognizing this issue. Veno-venous collaterals may allow a "pop-off" of venous blood from the SVC or pulmonary vascular bed to the IVC, decreasing blood flow to the lungs and negatively impacting systemic oxygen saturation. Echocardiography can detect many causes of refractory cyanosis. However, if venous collaterals, SVC or PA thrombosis, or a restrictive atrial septum are suspected, a diagnostic cardiac catheterization with the potential for intervention may be indicated. If diminished SCPC flow is believed to be due to increased PVR, treatment with oxygen or pulmonary vasodilators may prove beneficial. Patients with pre-existing lung disease often have pulmonary venous desaturation.

The "cavopulmonary–cerebral" circulation, referring to the connection of the SVC, which drains the cerebral circulation, to the PA, is an important physiological principle following SCPC (Figure 30.15). The transition to SCPC physiology is associated with increased cerebral oxygen saturation and a decrease in CBF velocity [175]. Because of the relatively large size of the young infant's brain and the responsiveness of CBF to $PaCO_2$, the $PaCO_2$ has an enhanced direct effect on PA flow after SCPC. A $PaCO_2$ of 40–45 mmHg results in improvements in cerebral and systemic oxygenation and systemic CO when compared with a $PaCO_2$ in the 30–35 mmHg range [170]. In the setting of a lower PaO_2 and SpO_2 than desired, appropriate $PaCO_2$ levels should be ensured. Among other benefits of early tracheal extubation, the mild elevation in $PaCO_2$ observed with spontaneous ventilation has significant advantages for the cavopulmonary–cerebral circulation. In addition, elevating the head 30–45° and maintaining a neutral neck position, without rotation, extension, or flexion, promotes optimal cerebrovenous drainage and improves oxygenation.

Systemic hypertension is another commonly observed problem early in the postoperative period. One of the proposed mechanisms for this phenomenon is the readjustment of the cerebral circulation to higher venous pressures after SCPC. Before SCPC, the cerebral venous pressure is usually 4–8 mmHg; after SCPC, SVC pressure is equal to PA pressure and is elevated to a mean of 12–18 mmHg. The CPP is thus reduced, and hypertension is thought to be a response to preserve CPP. Table 30.7 presents hemodynamic and oxygenation status problems and differential diagnosis in the early postoperative period after SCPC.

Special considerations exist for patients who require CPR or mechanical circulatory support (MCS) post-SCPC. Chest compressions will create systemic blood flow but little PBF in this patient subset, limiting oxygenation and CO. Adequate chest recoil will allow blood flow through the lungs and enhance flow from the IVC, providing preload [118].

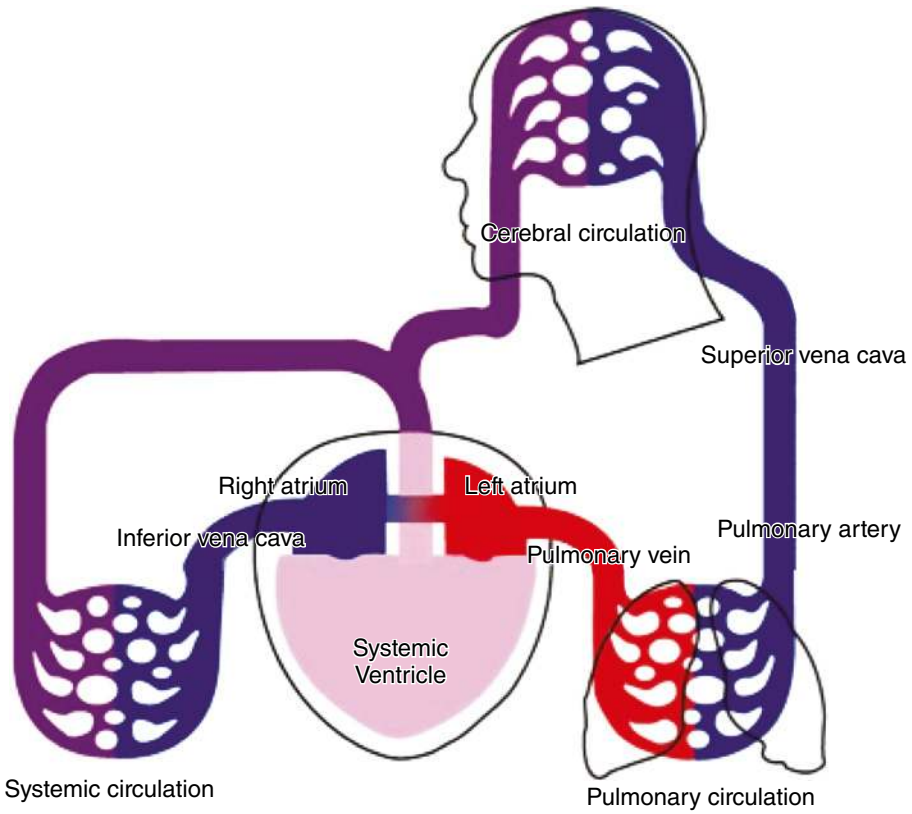


Figure 30.15 The cavopulmonary–cerebral circulation after superior cavopulmonary anastomosis. The relatively large brain of the young infant carries a large percentage of the cardiac output. Hyperventilation will decrease $PaCO_2$, constricting the cerebral arterioles and decreasing cerebral blood flow and cerebral oxygen saturation. This, in turn, decreases superior vena cava flow, decreasing pulmonary artery flow, which will lead to decreased systemic arterial oxygenation. (Source: Stephen A. Stayer, MD. Reproduced with permission.)

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Table 30.7 Hemodynamic status and differential diagnosis in the postoperative superior cavopulmonary anastomosis patient

Status	PAP (mmHg)	LAP (mmHg)	TPG (mmHg)	SpO_2 (%)	Etiologies
Normal	10–15	2–6	<10	80 ± 5	Ideal status
Elevated PAP	>15	2–6	>10	<75	High PVR; PA or PV obstruction
Elevated LAP	>15	>8–10	<10	<75	Ventricular systolic/diastolic dysfunction; sub-AS; AVVR; tamponade
Cyanosis	10–15	2–6	<10	<75	Decreased CBF; PV desaturation; decompressing veins; hypovolemia; anemia

PAP, pulmonary artery pressure as measured in the superior vena cava; LAP, left or common atrial pressure; TPG; transpulmonary pressure gradient (PAP–LAP); PVR, pulmonary vascular resistance; PV, pulmonary vein; AS, aortic stenosis; AVVR, atrioventricular valve regurgitation; CBF, cerebral blood flow.

Resultant elevations in SVC pressure and decreases in CPP will also increase the risk of subsequent neurological injury. Longer-term MCS is emerging as an option for SV patients after SCPC [176].

Outcomes

Overall outcomes following SCPC have been excellent in experienced centers, with a low early mortality rate of 3–4.7% [177]. Similar outcomes (mortality 4%) have also been reported for patients undergoing a comprehensive stage II procedure after an initial hybrid Stage I procedure [163]. A list of risk factors for complications, length of stay, and transplant-free survival has continued to evolve over the past decade [178]. Attrition between the SCPC and Fontan completion for HLHS patients has been reported to be independently associated with moderate or severe tricuspid valve regurgitation and low weight at the time of SCPC. Recent data from interstage home monitoring programs also indicate a continuing vulnerability and divergence in survival at 1 year for patients who required inpatient surveillance between their Stage I and II procedures [179].

KEY POINTS: SUPERIOR CAVOPULMONARY CONNECTION

- SCPC is generally performed between 3–6 months of age and is normally the second stage of palliation for SV patients.
- SCPC results in significant unloading of the systemic ventricle and stabilization of the circulation, particularly in HLHS.
- The creation of a "cavopulmonary–cerebral" circulation with SCPC is an important concept. Mild hypercarbia will promote cerebral and cavopulmonary blood flow, improving cerebral and systemic oxygenation and oxygen delivery.

Fontan completion

Surgical procedure

The Fontan procedure is the final stage in staged surgical single-ventricle palliation. The two Fontan variations currently used are the lateral tunnel (LT) and the extracardiac conduit (ECC), both also referred to as total cavopulmonary connection (TCPC) (see Figure 30.16). In earlier versions of the Fontan operation, the RA appendage was directly anastomosed to the PAs; this approach was known as an atriopulmonary Fontan and has been abandoned due to long-term adverse hemodynamic sequelae. These variations and conversion to modern Fontan configurations are discussed in Chapter 20.

The LT Fontan procedure is generally performed after the HF. After the institution of CPB with aortobicaval cannulation, moderate hypothermia and aortic cross-clamping are utilized. The RA is opened, the PTFE patch beneath the SVC-PA anastomosis is excised, and an intra-atrial PTFE tunnel is placed between the SVC-PA anastomosis and the orifice of the IVC [180]. Additional surgical procedures such as AVV repair, PA augmentation, atrial septectomy, and correction of residual coarctation can be performed simultaneously if necessary. Some surgeons create a 3–5 mm fenestration in the wall of the PTFE graft to permit blood flow from the higher pressure Fontan pathway to the lower pressure common atrial chamber (see Figure 30.17). Blood shunting via the fenestration to the common atrium augments CO, although this occurs at the expense of increased arterial desaturation due to the right-to-left shunt. As LT Fontan does not include circumferential graft material, pathway growth can occur, making the procedure possible in patients as young as 18 months of age.

In contrast, the ECC Fontan is generally performed following a BDG procedure. Mild hypothermic CPB is used, and aortic cross-clamping may not be necessary unless additional intracardiac procedures warrant its use. An 18–20 mm PTFE tube graft is sewn outside the heart, connecting the IVC directly to the underside of the right PA. As this tube graft will not grow, patient size is a consideration when performing an ECC Fontan. In some institutions, the ECC Fontan is performed with only partial right heart bypass, reducing circuit volume and obviating the need for blood transfusion in many patients [181]. The graft may be offset medially from the SVC–right PA anastomosis to improve flow dynamics so that IVC flow is preferentially directed to the left PA and SVC flow to the right PA. A potential drawback to this offset is that "hepatic factor" from the IVC may not perfuse the right PA, resulting in the development of PAVMs in the right lung. A fenestration may also be placed in the ECC configuration, though this is less commonly done to avoid arterial desaturation, ongoing risk of thromboembolism, and the potential need for intervention and fenestration

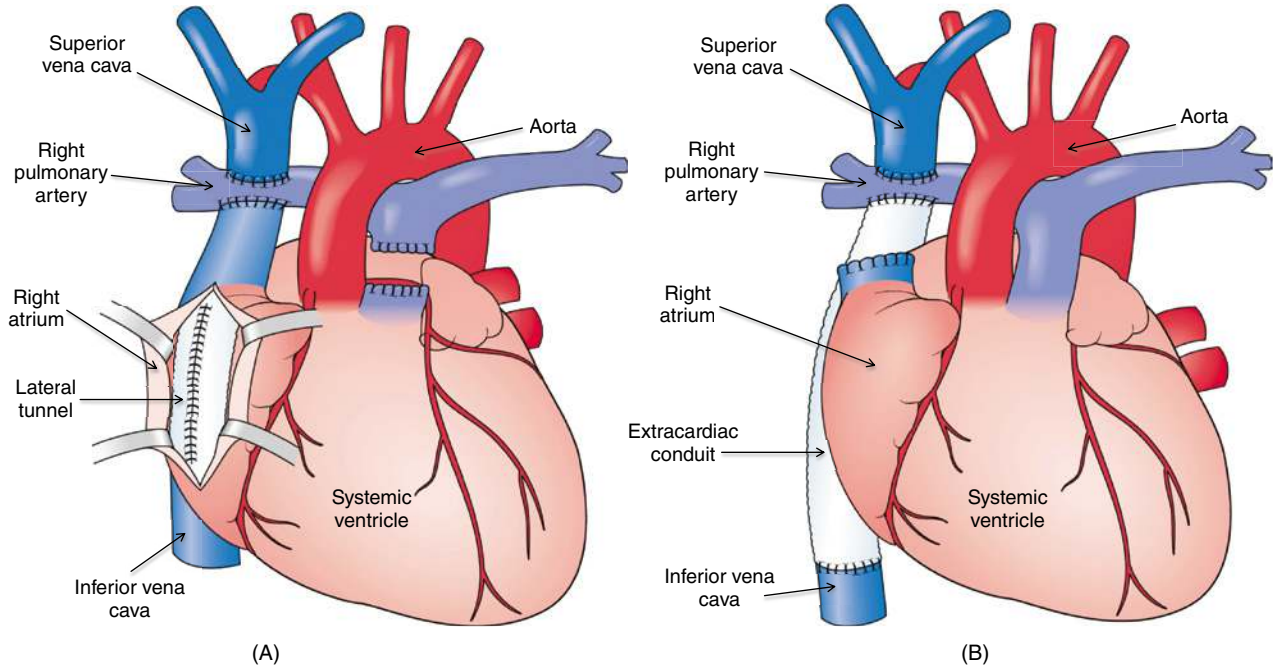


Figure 30.16 A lateral tunnel Fontan total cavopulmonary connection. (A) A polytetrafluoroethylene (PTFE) patch or tube is fashioned inside the right atrium. (B) Extracardiac conduit Fontan. The PTFE tube is anastomosed outside the heart from the detached inferior vena cava directly to the right pulmonary artery. (Source: Andropoulos et al. [35]. Reproduced with permission of Elsevier.)

closure at a future date. However, if the creation or enlargement of a fenestration becomes necessary in the future to treat Fontan failure or perform an electrophysiologic study, it is considerably more challenging to perform in an ECC Fontan due to anatomic considerations. A recent meta-analysis examining the effect of fenestration on outcomes demonstrated that having a fenestration reduced pulmonary pressure and reduced prolonged pleural drainage after the Fontan procedure, with no increased incidence of stroke observed. However, fenestration did not decrease the risk of Fontan failure, early death, or hospital stay after Fontan completion [182]. The intra/extracardiac conduit, a modification of the ECC Fontan, more easily permits the creation of a fenestration. This configuration alters the IVC connection to the ECC in that a small incision is made in the atrium, with the ECC then connected to the orifice of the IVC. A 4-mm fenestration is made in a short segment of the PTFE graft in the atrium before the ECC emerges out of the side of the atrium to continue to the PA anastomosis as in a standard ECC [183] (see Figure 30.18).

As the Fontan pathway is a low-flow system, optimizing fluid dynamics and minimizing energy loss is essential. Computational fluid dynamic models pioneered by de Leval have demonstrated hemodynamic performances of various Fontan anastomoses [184]. The combination of the HF followed by the Fontan procedure showed the lowest energy losses in a study by Bove et al. [185]. More recently, a Y-graft ECC Fontan, designed to allow more even distribution of hepatic blood flow, was shown over 3 years to significantly balance flow [186] (see Figure 30.19). To date, flow studies have still not definitively identified the best Fontan technique.

The choice between an ECC or LT Fontan is often institution or surgeon-specific and may also depend on the type of SCPC previously created. Early studies suggested that complications such as atrial arrhythmias and sinus node dysfunction might be due to intra-atrial suture lines and atrial manipulation during the creation of an LT Fontan [187, 188]. However, in a meta-analysis comparing early and long-term mortality, long-term arrhythmias, Fontan take-down, postoperative ventilation, ICU stay, thrombosis, and pleural or pericardial effusion, no differences were observed between patients with ECC or LT Fontan. The ECC Fontan patients had a lower incidence of supraventricular tachycardia 30 days post-Fontan and a lower rate of protein-losing enteropathy (PLE) compared with LT Fontan [189]. In 2020, an extensive retrospective analysis compared the LT and ECC techniques, finding that patients with LT Fontan had improved short- and mid-term survival and more extended freedom from Fontan failure compared with ECC Fontan patients [190]. Evidence has demonstrated that both procedures provide effective Fontan circulations with excellent outcomes.

Fontan physiology

The cardiovascular system in a biventricular patient has two circuits connected in series: pulmonary and systemic, each supplied with energy from a ventricular pump. In contrast, in SV patients after Fontan palliation, energy for both circuits must be provided by a single ventricular pump. After traversing the systemic circulation, the remaining energy in the systemic central veins must drive blood through the Fontan pathway and the pulmonary circulation. A visual of blood

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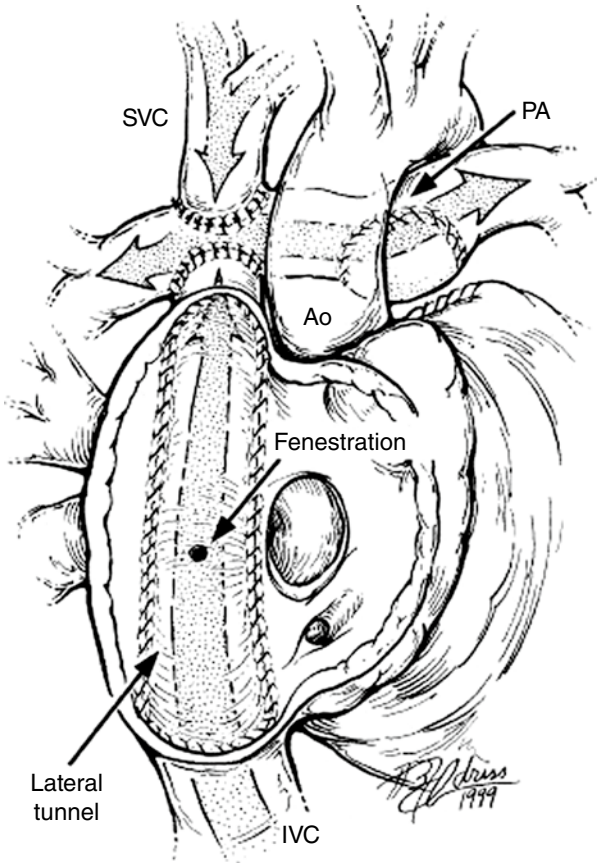


Figure 30.17 Lateral tunnel Fontan demonstrating a fenestration in the wall of the polytetrafluoroethylene tube that allows right-to-left blood flow from inside the Fontan circuit to the left atrial side. The fenestration is 3–5 mm in diameter and results in higher total cardiac output and oxygen delivery early in the postoperative course, at the expense of some arterial desaturation. (Source: Andropoulos et al. [35]. Reproduced with permission of Elsevier.)

traversing these different circulations is shown in Figure 30.20. Fontan physiology has two significant consequences that affect all Fontan patients to varying degrees: elevated CVP and diminished effective CO. As a result of these, a myriad of end-organ sequelae develop [191].

The TPG measures the pressure gradient driving blood from the central veins via the Fontan pathway through the lungs and into the common atrium. If PVR is elevated, blood flow through the lungs will be impeded, resulting in diminished ventricular filling and decreased CO. *The classic physiologic elements which control CO in a biventricular circulation – heart rate, preload, afterload, and contractility – do not do so in the Fontan circulation*. In a Fontan circulation, except for physiologic extremes such as significant tachycardia, bradycardia, or severe ventricular dysfunction, CO is determined by PBF [192].

This concept is modeled in Figure 30.21, which depicts differences between low, medium, and high PVR and the effects on CO [193]. Due to limited ventricular filling, CO in a Fontan patient is 70–80% of that expected for age and body surface area in a biventricular patient [194]. An inverse relationship exists between PVR and CO. Additionally, the benefit of increasing contractility in a Fontan circulation is limited, as greater contractility does not increase output when filling is limited.

Anesthetic considerations

Preoperative considerations

The Fontan pathway is a low-pressure system and is significantly affected by pressure elevations due to anatomic obstructions and resistance to flow. Ideal pre-Fontan characteristics include normal AV conduction, normal mean PAP, normal atrial pressure, normal systemic venous return, PVR <4 Woods units/BSA, PAs of adequate size that lack distortion, a competent AVV, and good ventricular function (see Table 30.8) [28].

Cardiac catheterization has been the traditional gold standard for preoperative assessment before the Fontan procedure, as not all SCPC patients are good candidates for Fontan completion. Criteria for cardiac catheterization include the following: patients with severe AVV or ventricular dysfunction, pulmonary vein stenosis, systemic obstruction, suspected pulmonary or SCPC obstruction, history of a complicated post-SCPC course, current oxygen saturation <75%, or suspected veno-venous or arteriopulmonary collaterals. Catheterization can provide information regarding the TPG, ventricular end-diastolic pressure, PVR, mean PA pressure, and common atrial pressure. However, cardiac catheterization is an invasive procedure utilizing ionizing radiation and, often, general anesthesia. Non-invasive imaging techniques such as cardiac MR or CT, along with echocardiography, can be used to assess low-risk patients who do not require presurgical intervention. These modalities also often require anesthesia or sedation. Fogel et al. compared the quality of information achieved in 410 patients utilizing cardiac MR, cardiac catheterization, or both. Diagnostic success was >95% in all three groups, and early post-surgical outcomes were equivalent. Significant radiation exposure was avoided in the cardiac MR patient group, but general anesthesia was used for this procedure [195].

Preoperative assessment should also include a review of the most recent cardiology visit and at-home medications. Management of anticoagulant medications often occurs in conjunction with the pediatric cardiologist. Patients whose medications include diuretics and afterload reducing agents should be advised to hold their day of procedure doses to decrease the risk of hemodynamic instability in the pre-CPB period. Additionally, information about prior sedative and anesthetic encounters, including airway management, should be ascertained.

Intraoperative considerations

Patients commonly present for Fontan completion between 18 months and 4 years, and as they have had many previous procedures, significant separation anxiety is not unusual. Anxiolysis may be achieved with midazolam, administered either orally or intranasally, or intranasal dexmedetomidine. It is helpful to review and discuss with the parents the history of the individual child's response to previous sedatives in order to choose the optimal premedication.

As with SCPC, anesthesia for Fontan completion can be induced with any of several IV or inhaled agents after the

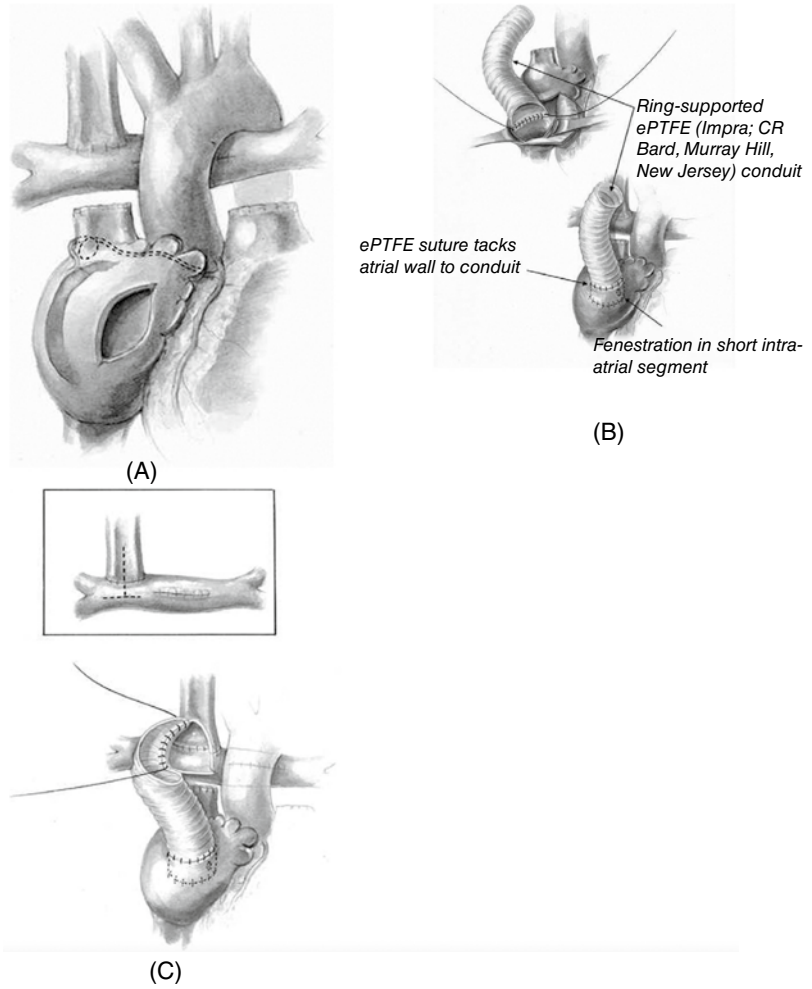


Figure 30.18 (A) The intra/extracardiac conduit fenestrated Fontan procedure incorporates an atrial incision that avoids injury to the sinus node, the sinus node artery and the crista terminalis. (B) A ring-supported ePTFE conduit is sutured to the internal orifice of the inferior vena cava. The short intra-atrial segment is fenestrated. A ePTFE suture tacks the atrial wall to the external surface of the conduit. (C) The beveled distal anastomosis of the intra/extracardiac conduit is usually fashioned to an inverted T incision that crosses the bidirectional Glenn anastomosis with extensions into the proximal and distal right pulmonary artery. (Source: Jonas [183]. Reproduced with permission of Elsevier.)

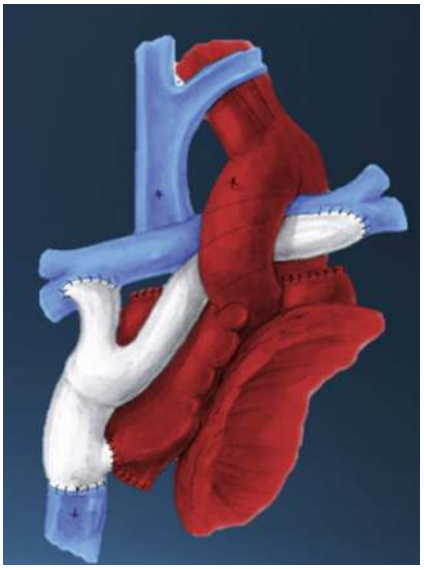


Figure 30.19 Extracardiac Fontan Y-graft. (Source: Trusty et al. [186]. Reproduced with permission of Elsevier.)

application of standard non-invasive monitors and NIRS monitoring. Unless myocardial dysfunction or unusual hemodynamic loading conditions (e.g., aortic arch obstruction or AV valve insufficiency) are present, SCPC patients generally tolerate the qualitative hemodynamic effects of anesthetic agents similarly to children without CHD. However, inhalation induction is slower due to the right-to-left shunting bypassing the lungs and delaying anesthetic uptake [196]. Some anesthesiologists prefer lower extremity peripheral IV access in patients with SCPC circulation as volume infused into an upper extremity IV will travel via the SVC into the pulmonary vascular bed before entering the common atrium. However, vascular access can prove challenging in patients with multiple prior procedures, and choices for placement may be limited. Cannulation of the IJ or subclavian vein is often used for central pressure monitoring, with the recognition that in SCPC patients, this catheter will measure PA pressure. The surgical team will usually place a transthoracic monitoring catheter in the common atrium to allow TPG calculation. Centrally located catheters are frequently removed early in the postoperative period to avoid the risk of thrombosis. During the pre-CPB period, the

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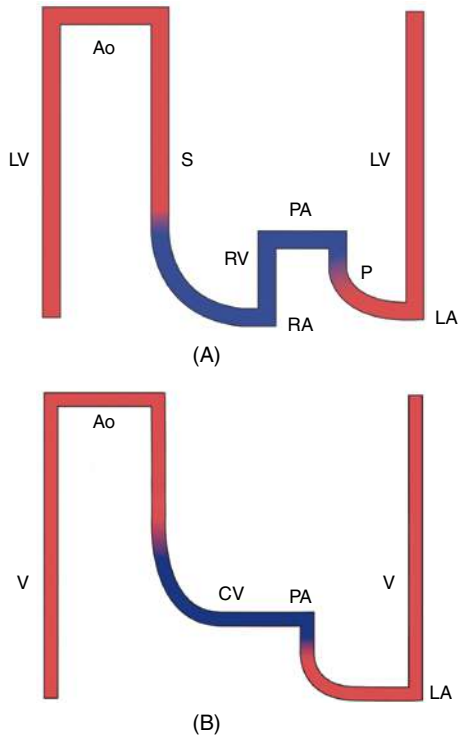


Figure 30.20 Scheme of the normal cardiovascular circulation (A), and the Fontan circulation at different stages B. (A) Normal biventricular circulation: the pulmonary circulation (P) is connected in series to the systemic circulation (S). The compliance of the right ventricle ensures that the right atrial pressure remains lower than the left atrial pressure and delivers the driving force to the blood to overcome pulmonary impedance. (B) Fontan circuit: the caval veins are directly connected to the PA; systemic venous pressures are markedly elevated. Ao, aorta; CV, caval veins; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; V, single ventricle. Line thickness reflects output, and color reflects oxygen saturation. (Source: Gewilig & Goldberg [193]. Reproduced with permission of Elsevier.)

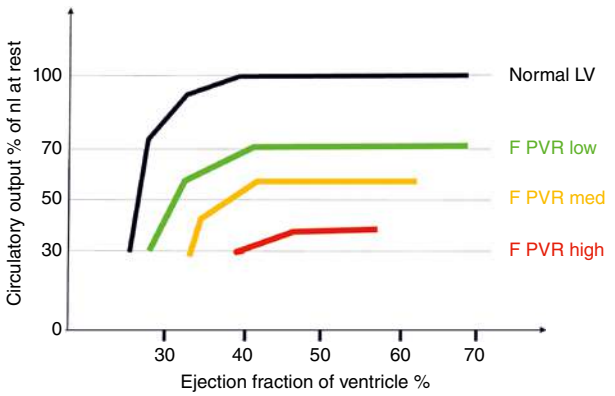


Figure 30.21 Output at rest modulated by pulmonary vascular resistance (PVR). In a normal subject (black line), the ventricular function has little effect on cardiac output except when very poor. The principal determinant of output in patients with Fontan circulation (colored lines) is the degree of the impedance of the pulmonary vasculature resistance (PVR). The higher the PVR (at rest), the lower the cardiac output even in the presence of normal systolic ventricular function; improving systolic function will have no influence on increasing cardiac output at rest. (Source: Gewilig & Goldberg [193]. Reproduced with permission of Elsevier.)

Table 30.8 Optimal pre-Fontan characteristics

Age <15 years
Normal atrioventricular conduction
Normal right atrial volume
Mean pulmonary artery pressure </ = 15 mmHg
Normal systemic venous return
PVR <4 wood units/m² BSA
No pulmonary artery distortion
Pulmonary artery: aortic diameter ratio > / = 0.75
Competent systemic atrioventricular valve
Left ventricular ejection fraction > / = 0.6

Source: Roeleveld et al. [28]. Reproduced with permission of Cambridge University Press.

SCPC circulation remains dependent on blood return from the SVC to provide PBF. As hyperventilation can decrease CBF, hypocarbia should be avoided and maintenance of normocarbia or mild hypercarbia should be the goal. As patients presenting for Fontan palliation have had prior sternotomies, the potential for significant bleeding upon entering the thoracic cavity exists and appropriate precautions should be in place.

A balanced technique combining inhaled sevoflurane, opioid, and neuromuscular blockade is commonly used for anesthetic maintenance. The total opioid dose is often limited to the equivalent of fentanyl 7–15 mcg/kg to facilitate the goal of sufficient emergence from anesthesia to permit tracheal extubation in the OR or soon after arrival in the cardiac ICU. Due to its analgesic and sedative properties, as well as a favorable hemodynamic profile, the use of a dexmedetomidine infusion has become the mainstay in the cardiac OR and it is frequently continued postoperatively in the ICU as well.

Epidural opioids administered via the caudal route have been used by some institutions to facilitate analgesia and early tracheal extubation. A prospective, randomized, double-blind study comparing caudal morphine (100 mcg/kg before incision) with saline placebo found no difference between groups in achieving either extubation within 30 minutes of surgical end time or freedom from reintubation within 24 hours. The authors concluded that early extubation was feasible for most patients with or without caudal morphine [197]. Recently interest has grown in using regional blocks as part of a multimodal approach to postoperative pain management in pediatric cardiac surgery patients [198]. These techniques avoid concerns regarding the risk of epidural hematoma with central neuraxial blocks in cardiac surgery patients undergoing full heparinization. However, to date, no data exist specifically examining these techniques in patients undergoing the Fontan procedure.

Children entering the OR have SCPC circulation and are cyanotic to varying degrees. The compensatory polycythemic response to cyanosis leads to higher hemoglobin levels to increase oxygen-carrying capacity, and some patients may not require a blood transfusion during the Fontan procedure. Thromboelastography or thromboelastometry are often used to measure routine coagulation parameters and guide the use of specific clotting products. The immediate results from the Fontan operation should be the improvement of systemic oxygenation, with an accompanying higher CVP. Post-CPB management should include volume resuscitation to ensure

adequate CVP to support the Fontan circulation, meticulous attention to ventilation to minimize PVR, low-dose inotropic support, and rapid restoration of hemostasis. As noted previously, PEEP is employed only as necessary at physiologic levels to preserve normal FRC. The Fontan operation is well tolerated by the majority of children. Despite this usual stable course in the operating room, some Fontan patients have prolonged chest tube drainage postoperatively, which can lengthen hospital stay. Vasopressin infusion started in the operating room after CPB and continued for 24–48 hours postoperatively has been reported to reduce chest tube drainage, transpulmonary gradient, postoperative fluid administration, and days chest tubes are indwelling [199, 200]. A number of institutions have added vasopressin to their immediate postoperative regimen for the Fontan operation.

Positive pressure ventilation increases intrathoracic pressure, causing a decrease in central venous inflow. Spontaneous ventilation increases central venous filling, increasing blood flow through the Fontan pathway into the lungs. The avoidance of prolonged postoperative PPV should be a routine strategy for patients with Fontan physiology. In a retrospective study, the duration of CPB did not impact the ability to safely extubate patients within 6 hours post-Fontan. The early extubation group had higher mean arterial pressure and lower mean pulmonary pressure at 6, 24, and 48 hours postoperatively compared with the group with prolonged intubation, leading the authors to conclude that early extubation should be a primary aim to improve postoperative Fontan outcomes [201]. Another retrospective study examined 253 patients before and after a programmatic change to extubate all Fontans within 12 hours postoperatively regardless of hemodynamic status, challenging a standard convention of avoiding early extubation in less stable patients. "Instability" was defined as having higher postoperative inotropic scores and volume requirements. Successful extubation was possible in all patients, although a higher reintubation rate was observed in unstable patients. Extubation in the unstable patients ($n = 50$) led to an acute rise in mean arterial pressure and decreases in the inotropic score and volume requirement [202].

Postoperative considerations

Diminished PBF after the Fontan operation will cause reduced CO, unlike SCPC physiology, in which decreases in PBF result in reduced systemic oxygen saturation. Extreme vigilance is required to maintain adequate intravascular volume in the setting of ongoing blood loss in the early postoperative period. Avoidance of any elevation in PVR is essential. A fenestration may ameliorate some early postoperative hemodynamic instability but will lead to arterial desaturation as deoxygenated blood in the Fontan pathway shunts right-to-left into the common atrium, effectively adding ventricular preload. The use of low ventilatory pressures with early extubation should be the aim.

Systemic oxygenation saturation should be near normal in the postoperative period in a patient without a fenestration. A modest degree of hypoxemia can be expected due to a fenestration along with coronary sinus blood flow, which usually enters the common atrium on what is functionally the pulmonary venous side. Persistent systemic oxygen saturation less than 85–90% can result from one or more of the following causes: (i) greater fenestration flow than anticipated; (ii) lung pathology; (iii) venovenous collaterals; (iv) PAVMs causing intrapulmonary shunting; or (v) increases in oxygen demand as seen with decreased CO or sepsis. Differentiating between these concerns can require cardiac catheterization.

Myocardial dysfunction typically follows the same differential described previously for post-SCPC. Hemodynamic etiologies should be investigated and corrected. However, myocardial dysfunction may also occur as the result of inadequate myocardial preservation, coronary perfusion, or a metabolic process. In the absence of correctable causes such as hypocalcemia, supportive measures represent the mainstay of therapy. Postoperative arrhythmias can occur, and while heart block is uncommon, junctional rhythm may occur in up to 25% of patients. If the escape rate is low enough to cause hemodynamic instability, the use of epicardial, atrial, or AV pacing usually proves beneficial. Tachyarrhythmias are less common in the early postoperative period but are more likely to have a negative hemodynamic impact when present. Doppler interrogations of PBF patterns suggest that diastolic flow is best under normal circumstances [203], perhaps explaining the intolerance of tachyarrhythmias. Alternatively, unfavorable hemodynamics may serve to provoke tachyarrhythmias. Table 30.9 presents the differential diagnosis for low SpO_2 and blood pressure in the postoperative Fontan patient.

Several risk factors have been identified that can predict prolonged ICU length of stay, which is, in turn, associated with late mortality and the need for late cardiac reoperation. Pre-existing anatomic risk factors include HLHS, anomalous systemic venous drainage, heterotaxy, and systemic RV. Preoperative predictive factors are higher preoperative hemoglobin and low preoperative oxygen saturation, elevated PAP, and high preoperative TPG. Identified postoperative risk factors include pleural effusion, chylothorax, ascites, and infection [204–206].

Long term complications and outcomes

Long-term survival has improved significantly since the Fontan procedure was initially described in 1971 [1]. Early atriopulmonary Fontan patients have demonstrated worse long-term outcomes than those with the contemporary forms of TCPC, with a recent study describing only 45% of atriopulmonary Fontan patients free from heart failure, transplantation, or death at 28-year follow-up [207]. Patients undergoing Fontan completion in the current era have an approximate 30-year survival of 85% [208]. However, the quality of these years can be variable, with half of the patients experiencing a major adverse event before 14 years of age [209]. However, a recent study from the Australia and New Zealand Fontan Registry examined patients without a single complicating event before age 16; this included nearly 75% of their Fontan population. Survival in this group was 94% at 30 years, and projection models suggested potential survival for this low-risk cohort at 60 years to be 49–67% [210].

A meta-analysis evaluating risk factors for late Fontan failure and death found >80% of patients alive 20 years post-Fontan. Risk factors for late death included PLE, increased

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Table 30.9 Hemodynamic status and differential diagnosis of abnormalities in the postoperative Fontan patient

Status	PAP (mmHg)	LAP (mmHg)	TPG (mmHg)	Systolic BP (mmHg)	SpO_2	Etiology
Normal	10–15	2–6	<10	85–95	95 ± 5	Ideal status
Decreased PAP and LAP	8–10	0–4	<10	<80	90 ± 5	Hypovolemia
Elevated PAP	>15	2–6	>10	80 ± 5	90 ± 5	High PVR; PA or PV obstruction
Elevated LAP	>15	>8–10	<10	80 ± 5	90 ± 5	Ventricular systolic/diastolic dysfunction; AV dissociation; AVVR; tamponade
Cyanosis	10–15	2–6	<10	85–95	<85%	Excessive fenestration size or Fontan baffle leak; PV desaturation; decompressing veins; hypovolemia; anemia

AS, aortic stenosis; AVVR, atrioventricular valve regurgitation; LAP, left or common atrial pressure; (PAP–LAP); SpO2, pulse oximeter saturation; PAP, pulmonary artery pressure as measured in the superior vena cava; PV, pulmonary vein; PVR, pulmonary vascular resistance; TPG, transpulmonary pressure gradient.

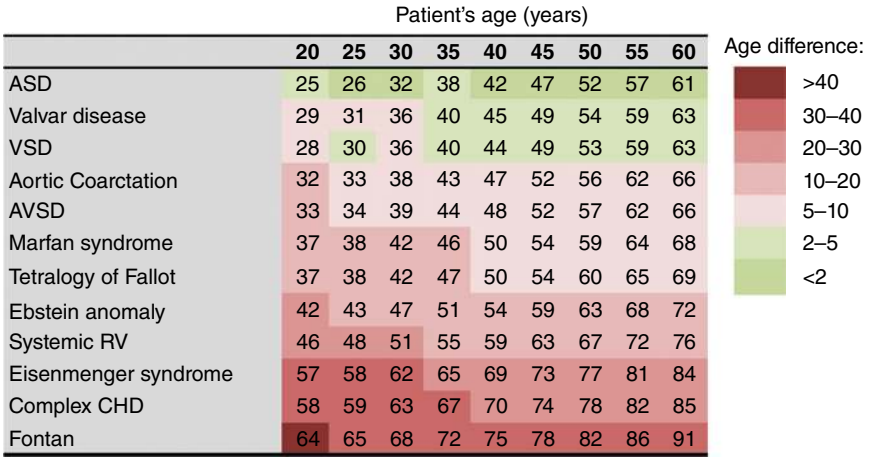


Figure 30.22 Mortality in subgroups of patients compared with mortality in the age-matched United Kingdom (UK) population. Numbers on the colored surface present the equivalent age – expressed as the age of subgroup of UK population, having similar 5-year mortality rates. Colors reflect the difference between the relative age and the actual age of patients. The curved line corresponds to the 5-year risk of death of the general UK population according to life table data. ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart disease; RV, right ventricle; and VSD, ventricular septal defect. (Source: Diller et al. [212]. Reproduced with permission of Wolters Kluwer Health, Inc.)

end-diastolic volume (as a surrogate for ventricular dysfunction), and the need for a pacemaker. Causes of death were late Fontan failure (34%), sudden death (19%), and perioperative death (16%). Survival post-Fontan at 5, 10, and 20 years was 95, 91, and 82% [211]. Overall, in calculating life expectancies for congenital heart defects, the life expectancy for a 20-year-old Fontan patient was estimated to be equivalent to that of a 64-year-old without heart disease [212] (see Figure 30.22).

Significant morbidity in Fontan patients can include heart failure, AVVR, arrhythmias, thrombotic events, lymphatic dysfunction causing PLE and plastic bronchitis (PB), chronic venous insufficiency, renal disease, Fontan-associated liver disease (FALD), and neurocognitive and psychosocial issues. An increase in PVR normally occurs with aging, and for Fontan patients, this has significant implications. Increased filling pressure accompanying the increasing PVR over time can lead to more substantial decreases in CO and Fontan failure, as shown in Figure 30.23 below [213].

Heart failure can be classified as either classic pump failure or failure of the Fontan circulation with elevated CVP and diminished CO but preserved function. Many patients have elements of both. Heart failure predicts poor outcomes, with a 1-year mortality of 24% and 3-year mortality of 35% [214]. Evidence is lacking to support the use of standard heart failure medications in Fontan patients, and concerns exist that vasodilators and diuretics could worsen heart failure in patients with Fontan physiology. However, afterload reduction agents and diuretics are widely used to treat Fontan failure [215]. A study examined sildenafil in a double-blinded, placebo-controlled, crossover trial of 27 healthy Fontan outpatients, finding that global ventricular performance and measures of CO improved, although diastolic function did not change [216]. Phosphodiesterase-5 inhibitors and endothelin-1 inhibitors are commonly used to treat Fontan failure.

Atrioventricular valve regurgitation contributes to long-term morbidity and mortality in Fontan patients, causing

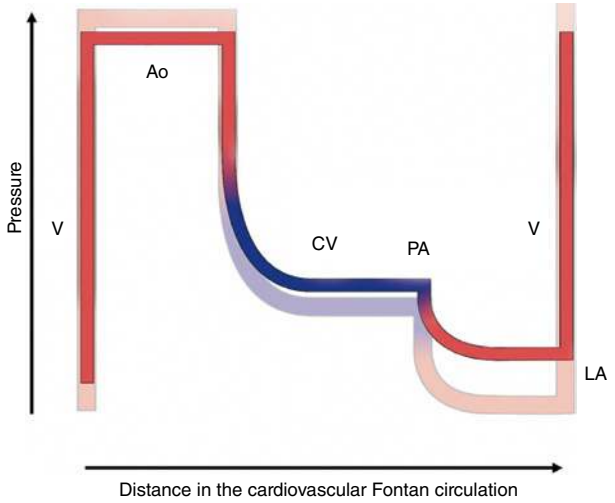


Figure 30.23 Flow/pressure/saturation diagram of the Fontan circulation: changes over time. Fontan haemodynamics late (full color) superimposed on Fontan early (transparent): with time the ventricular end-diastolic pressure and pulmonary vascular resistance increase, resulting in overall decreased flow and increased caval vein pressure/congestion. A downward progressive spiral ensues. Ao, aorta; CV, caval veins; LA, left atrium; PA, pulmonary artery; V, single ventricle. (Source: Gewillig et al. [213]. Reproduced with permission of John Wiley & Sons.)

Fontan failure at twice the rate compared with patients who do not have AVVR. One third of patients will require AVV repair by age 30 years. Atrioventricular valve regurgitation can lead to ventricular dysfunction or may itself be caused by ventricular failure. Diuretics and afterload reducing agents are frequently utilized, although solid evidence for this therapy is lacking. Optimal timing of valve repair and when and if valve replacement should occur remain unknown [217].

Arrhythmias are a common complication of Fontan surgery, with a recent study finding an incidence of 18.9% [218]. In the early postoperative period, AVVR is a risk factor for arrhythmias, and later, older age at Fontan and high PAP become predictors [219]. Arrhythmia development is an independent risk factor for late Fontan failure and has not been shown to be related to the type of Fontan (LT or ECC). Forty percent of patients with arrhythmias developed reduced ventricular function within 10 years. Ablation was effective, with 50% of patients arrhythmia-free at 10 years post-ablation [218]. Up to 25% of patients with a Fontan require epicardial pacing to manage late arrhythmias [220].

The incidence of thrombosis in one study of 111 patients was 31% at 2.5 years. The risk of thrombosis is highest immediately postoperatively, but the ongoing lifelong risk exists. Prolonged presence of a central line, uncontrolled warfarin use, and lower fraction of inspired oxygen use are all risk factors for postoperative thrombosis [221]. Many cardiologists treat low-risk Fontan patients with antiplatelet medications and add warfarin for higher-risk patients. Currently, standardized anticoagulation guidelines are lacking.

Fontan-associated liver disease is likely related to chronically high CVP and diminished effective CO. Hepatic stiffness has been shown to occur immediately after the Fontan operation [222]. The liver, despite its dual blood supply, can be compromised when decreased CO results in decreased hepatic arterial flow as the portal system cannot compensate due to a lack of autoregulation. The liver may then be especially susceptible to hemodynamic insults [223]. Liver biopsy remains the gold standard for assessing liver dysfunction. However, this is an invasive procedure and incurs the risk of bleeding as well as sedation and anesthesia risks. A recent study using ultrasound-guided percutaneous liver biopsy in patients at least 10 years post-Fontan demonstrated that hepatic fibrosis is a universal characteristic of Fontan physiology. Fontan hemodynamics, ventricular function, and AVVR were not associated with the degree of fibrosis [224]. Over time, hepatic fibrosis may progress to cirrhosis and hepatic failure. In another study of prospective hepatic screening for Fontan patients >18 years old, 50% were found to have varices, and 25% had hyper-enhancing liver nodules. Routine imaging, elastography, and biomarkers were unable to assess the severity of liver fibrosis accurately [225]. Hepatocellular carcinoma has been reported in young Fontan patients. These findings indicate that ongoing hepatic surveillance is necessary for Fontan patients, but no consensus guidelines currently exist.

The renal system is at risk as well, with a retrospective study showing that acute kidney injury (AKI) was present in 42% of patients post-Fontan. Independent predictors of AKI included lower renal perfusion pressure and higher inotrope score [226]. Using a stringent AKI definition in a prospective study of adult patients with an average age of 28.4 years, 46% had evidence of chronic kidney disease, suggesting that long-term follow-up of renal function in Fontan patients is also essential [227].

Patients with Fontan circulation might also be expected to experience a range of psycho-social- neurocognitive challenges due to frequent hospitalizations and surgeries and the effects of living with a chronic disease. A recent meta-analysis examining patients and parent-proxies reporting on the quality of life of children, adolescents, and adults with Fontan physiology showed that health-related quality of life (HRQOL) was lower in patients with Fontan physiology than the general population, with the most significant differences being physical functioning and school/work functioning. Older age at the time of Fontan was associated with worse emotional HRQOL, and HLHS was associated with lower social HRQOL [228].

Protein-losing enteropathy and plastic bronchitis

Protein-losing enteropathy (PLE) and PB are two relatively rare complications with a combined incidence of 4.9% at 30 years and 7.4% at 35 years post-Fontan operation. Freedom from death or transplantation at 5, 10, and 15 years after diagnosis was 70, 65, and 43%, respectively [229]. Protein-losing enteropathy causes leakage of protein-containing lymphatic fluid into the intestinal lumen. Specific loss of albumin, anticoagulant proteins, and immunoglobulins can result in ascites, malnutrition, thrombosis, and infection. Plastic bronchitis is characterized by leakage of proteinaceous lymphatic fluid into the bronchial tree. This leakage can solidify into casts, which are then coughed out or can result in airway obstruction. Patients typically have a chronic cough and

hypoxemia. With the onset of either PLE or PB, evaluation of the Fontan circulation should be undertaken to rule out any anatomic obstructions. Pulmonary vasodilators, along with diuretics, may be used to treat both PLE and PB.

The altered hemodynamics of patients with Fontan physiology affect the morphology and function of the lymphatic system, rendering this population prone to the development of lymphatic complications, including PB, PLE, chylous pleural effusions, and ascites. The primary circulatory role of the lymphatic system is to transport fluid from the tissues back to the venous system via lymphovenous connections. Despite awareness of this role for many years, lymphatic flow pathophysiology has been poorly understood due to a lack of reliable non-invasive lymphatic imaging techniques. This has limited treatment options, resulting in significant morbidity and mortality. Two specific factors exist and contribute to pathologic findings: increased lymph flow in patients with chronically elevated CVP due to BDG, HF, or Fontan physiology, and lymphatic anatomical variants that allow lymph flow near serous (pleural space in chylothorax) or mucosal (PB, PLE) surfaces. Recently developed intranodal (inguinal, liver, and mesenteric) lymphangiography and dynamic contrast-enhanced MR lymphangiography have enabled visualization of the central lymphatic anatomy and flow dynamics with high resolution, enabling elucidation of the mechanism behind these conditions.

In patients with PB imaging demonstrates retrograde lymphatic flow from the thoracic duct (TD) toward the lung parenchyma. Embolization or TD stenting with covered stents to exclude retrograde flow to the lungs and eliminate lympho-bronchial airway communication has resulted in durable remission of the disease, including at least temporary cessation of cast formation in a high percentage of patients [230] (see Figure 30.24). In patients with PLE, liver lymphangiography demonstrates leakage of liver lymph into the duodenum through abnormal hepatoduodenal lymphatic communications. Liver lymphatic embolization with lipiodol (ethiodized oil) or glue (cyanoacrylate) has resulted in improvement of symptoms and an increase in serum albumin levels in a significant number of patients [231].

Although embolization of abnormal lymphatics has improved outcomes for some, alternative treatment strategies have been proposed to enhance lymphatic drainage while leaving the lymphatic system intact. Diverting lymph drainage to the low-pressure pulmonary venous atrium is one treatment that may also prevent or decrease end-organ fibrosis or failure, although at the expense of increased cyanosis. This has been accomplished via catheter-based or surgical re-routing of the innominate vein and TD to the low-pressure atrium (Figure 30.25) [232]. The micro-surgical creation of lymphovenous anastomoses is another treatment option.

Consideration should be given to using T2 weighted MR imaging sequences to assess lymphatic perfusion abnormalities in all patients after completing the SCPC to risk-stratify patients before Fontan. Patients with high-grade lymphatic abnormalities had six times greater odds of developing early lymphatic complications, longer lengths of stay, and an increased likelihood of Fontan failure [233]. Prophylactic innominate vein turndown may be considered at the time of the Fontan for patients who are at high risk for lymphatic complications. If imaging is not feasible or deemed not necessary in all patients, imaging should be applied early in the course of symptomatic lymphatic disorders, which may prevent progressive debilitation when these complications go untreated.

Anesthetic considerations for lymphatic intervention

Many of the current population presenting for lymphatic procedures have had lymphatic flow abnormalities for months or years that have been unresponsive to medical therapies. As a result, many have a significant functional impairment and poor quality of life due to longstanding lymphatic loss and replacement. The outcome for these patients without effective treatment is increasing morbidity and, for some, death.

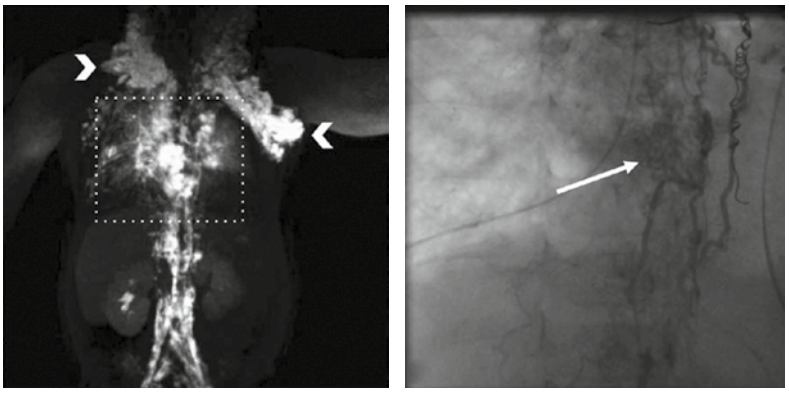


Figure 30.24 MIP of DCMRL (A) and lymphangiogram (B) images of the central lymphatic system of a patient with type 5 PB. (A) MIP of the DCMRL shows diffuse perfusion of both lung fields (box). Also seen are the filling of cervical and left-sided axillary lymphatic networks (arrow heads). (B) No identifiable TD is seen, but, instead, multiple dilated ducts are seen supplying both lungs (arrow). DCMRL indicates dynamic contrast-enhanced magnetic resonance lymphangiogram; MIP, maximum intensity projection; PB, plastic bronchitis; and TD, thoracic duct. (Source: Dori et al. [230]. Reproduced with permission of Wolters Kluwer Health Inc.)

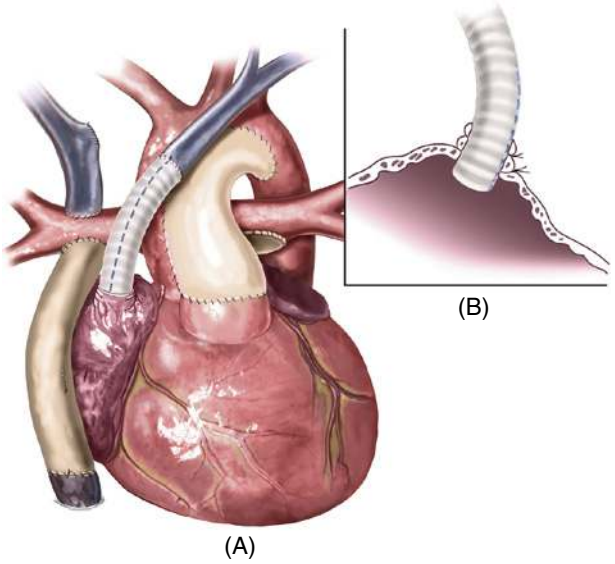


Figure 30.25 Innominate vein turndown with an interposition graft. (A) Graft from distal innominate vein to right atrial appendage with a ringed polytetrafluoroethylene graft. (B) "Dunk" technique with 3–4 rings inserted inside the atrium to prevent obstruction. This technique can also be accomplished without a graft by direct anastomosis to the left atrial appendage. Postoperative system oxygen saturations often decrease by about 5% due to the creation of a veno-venous shunt. (Source: Hraska et al. [232]. Reproduced with permission of Elsevier.)

Thus, practitioners, patients, and families are willing to accept the risks of anesthesia and lymphatic interventions.

Assessment of intravascular fluid volume status is essential in patients with drainage tubes for pleural effusion or ascites and those receiving diuretics. Failure to correct hypovolemia will result in systemic hypotension due to vasodilation from anesthetics and reduction of venous return from PPV. Many patients with ongoing drainage have resultant hypoalbuminemia, resulting in partial protein binding and increased free drug with consequent greater potency. Chronic steroid therapy can result in adrenal suppression, and these patients require stress-dose steroids before anesthesia.

An essential component of anesthetic management involves preventing patient movement that could dislodge precisely placed needles or catheters during imaging, intervention, or transport of patients between catheterization laboratory or interventional radiology suite and MRI. Sedation alone is not adequate due to the duration of the procedures and respiratory and circulatory compromise from lymphatic pathology and other comorbidities. Concurrent ancillary procedures, including cardiac catheterization, bronchoscopy, endoscopy, vascular access, and drain placement, also require general anesthesia. Given these considerations, general endotracheal anesthesia with neuromuscular blockade is preferred. Casts in patients with PB can completely obstruct the trachea or endotracheal tube after induction of anesthesia, and consideration should be given to routine bronchoscopy and removal of casts immediately after intubation. A urinary drainage catheter is placed to prevent bladder distention and increased abdominal pressure during lengthy procedures. It is also helpful as cardiac catheterization with angiography is performed, and a full bladder may obstruct visualization of the lower pelvic lymphatic pathways. Careful body positioning and pressure point padding are necessary as later adjustments cannot be made once needles are placed in the lymph nodes. Monitoring and maintenance of body temperature are critical. Administration of IV antibiotics before needle placement and interventions is necessary due to trans-abdominal passage of needles through the gastrointestinal (GI) tract.

Access to both radiologic imaging and MRI requires the transportation of anesthetized patients. When separated by distance, IV anesthesia and manual ventilation along with a transport monitor are used. A wheeled transport table mated to both the X-ray and MRI tables maintains patient immobility. Scheduling must be coordinated among multiple disciplines, including anesthesia, radiology, cardiology, and depending on the lymphatic issues, pulmonary and gastroenterology.

Post-procedure, it is recommended that all patients undergoing lymphatic intervention be admitted to the ICU for observation as an escalation of care or complications (fever, hypotension, bleeding, stroke) occur in approximately 25% of patients in the first 24 hours post-procedure [234]. In most patients, postprocedural mechanical ventilation is unnecessary unless it was required preprocedurally. Abdominal pain is common after trans-abdominal needle passages. Patients are monitored for infection and bleeding from needles passing through intra-abdominal blood vessels, liver, GI tract, and bile ducts. A percentage of patients will manifest a systemic inflammatory response requiring IV fluids, inotropic agents, and/or vasoconstrictors for stabilization. Neurologic status is monitored for systemic embolization of endovascular glue or lipiodol in patients with right-to-left shunts.

Pregnancy

Up to 70,000 patients with a Fontan circulation are estimated to be alive today, with that number expected to double in 20 years. For women with Fontan physiology, common maternal cardiovascular events during pregnancy can include supraventricular arrhythmias (8.4%) and heart failure (3.9%), with heart failure also occurring in the postpartum period. One study found that most (89%) received anticoagulant therapy, and Caesarean-section was performed in 57.1% of pregnancies. Fifty-nine percent of the babies were premature, 20% were small for gestational age, and 5% died in the neonatal period. Further reviews with larger patient populations and longer follow-up are needed to assess late sequelae of pregnancy in Fontan patients [235]. Further discussion of pregnancy after Fontan operation is presented in Chapter 20.

Mechanical circulatory support

Interest and experience continue to grow regarding MCS as a bridge to transplant or as destination therapy for failing Fontan patients, but no large studies exist offering established guidelines for MCS use in this population. Mechanical circulatory support is indicated when the Fontan circulation has failed to maintain adequate oxygenation and CO despite maximal medical therapy. Ideally, with MCS, improvement can occur in end-organ, nutritional, and physical function which will improve the patient's health and likely make cardiac transplantation more successful

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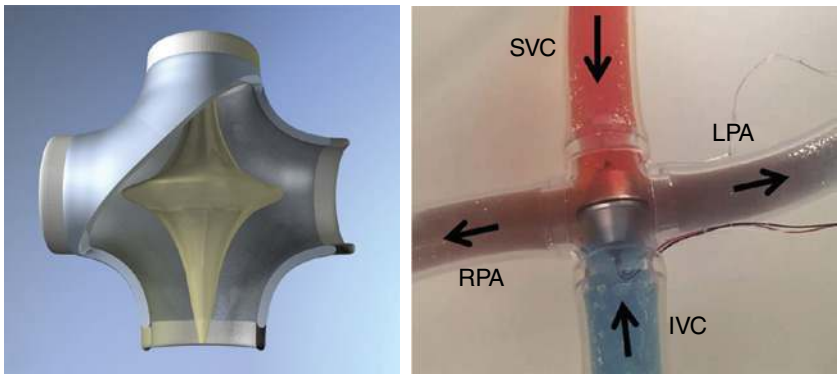


Figure 30.26 Implantable cavopulmonary assist device. (A) Conceptual image. A central impeller contains the motor (impeller support shaft and struts not shown). The external housing is a thin-walled, hard case shell that has no component bulk and serves only to direct Fontan flow. The wide gap between the impeller and the housing must support passive total cavopulmonary connection flow at low resistance in the event of device dysfunction. (B) Advanced prototype image depicting pump function. Color contrast demonstrates superior vena caval (SVC) flow (red) and inferior vena caval (IVC) flow (blue) mixing to both left pulmonary arterial (LPA) and right pulmonary arterial (RPA) outlets (purple). (Source: Rodefeld et al. [237]. Reproduced with permission of Elsevier.)

[236]. Due to patient variability, each patient must be considered individually. Patients with ventricular dysfunction may benefit from a ventricular assist device (VAD), while patients with preserved ventricular function but circulation failure may benefit from a total artificial heart (TAH). Extracorporeal membrane oxygenation may offer a temporary solution. Future options may also include a cavopulmonary assist device. One such device currently being developed is a rotary motor placed into the Fontan pathway to propel blood through the pulmonary circulation (see Figure 30.26) [237].

Specific anesthetic goals, similar to managing any patient with poor ventricular function, include cautious use of induction agents, use of a balanced technique (narcotic, low levels of inhalational agent, and dexmedetomidine), and readiness to treat hemodynamic instability. As patients have previously had multiple sternotomies and have poor functional status and high bleeding potential, these surgeries are complicated and lengthy. Weaning from CPB should include the use of TEE to ensure a nondilated, well-filled ventricle with CVP in the low teens and mean arterial pressure in the 60–70 mmHg [238]. The use of coagulation products is guided by thromboelastography or thromboelastometry. Post-VAD placement, PBF can be maintained with the use of iNO and milrinone. Hemodynamics may be supported with norepinephrine, epinephrine, and, if necessary, vasopressin. The goal should be to achieve early postoperative spontaneous ventilation and early extubation if possible [239]. Patients with MCS are often anticoagulated with heparin or unfractionated heparin. More recently, bivalirudin, a competitive, reversible thrombin inhibitor that prevents thrombin activation of fibrinogen to fibrin, has been used. Bivalirudin may be administered as a continuous infusion with dosing based on PTT [240]. After the immediate postoperative period, patients are often transitioned to warfarin and aspirin. A reasonable estimate of survival in a Fontan patient requiring MCS is about 60% [238]. See Chapter 37 for further discussion of mechanical circulatory support.

Cardiac arrest in the Fontan patient

Survival after cardiac arrest in a patient with Fontan physiology is approximately 60% [119]. This low survival is likely due to specific characteristics of the Fontan circulation. Maintenance of some coronary and cerebral pressure during CPR is essential to minimize neurologic injury and mortality. However, in a Fontan patient, during chest compressions, CVP increases, with a resultant decrease in CPP as well as a decrease in venous return. The reduction in venous return will decrease flow through the pulmonary vasculature, decrease ventricular filling, and ultimately decrease CO. In addition, the acidosis which occurs during CPR will cause elevations in PVR, further limiting PBF. Conversion from CPR to ECMO can be challenging in a Fontan patient and almost impossible to perform expeditiously via central vessels in a patient with a well-healed sternum. Peripheral cannulation is difficult due to access-related issues and the need to cannulate both upper and lower extremity venous vessels to decompress the Fontan pathway. Although it may be performed instead of central cannulation it may not allow the adequate circuit blood flow required with a failing, non-ejecting ventricle. As CPR and emergent use of ECMO have poor outcomes, early elective ECMO cannulation should be considered if the potential for reversibility exists. In a study of 230 Fontan patients experiencing cardiac arrest, 35% survived to discharge [241]. See Chapter 25 for further discussion of cardiac arrest and resuscitation.

KEY POINTS: FONTAN COMPLETION

- The Fontan, or TCPC, is the final palliation for single-ventricle anatomy and is normally performed at 18 months to 4 years of age.
- The two contemporary Fontan configurations utilized are the intra-atrial lateral tunnel and the extracardiac conduit.

- A fenestration can be created to lower cavopulmonary pressure and improve systemic CO, at the expense of some arterial desaturation.
- PPV, hypovolemia, and loss of AV synchrony are all detrimental to the Fontan circulation because of the lack of a pulmonary ventricle.
- The classic physiologic elements which control CO in a biventricular circulation – heart rate, preload, afterload, and contractility – do not do so in the Fontan circulation. In a Fontan circulation, except for physiologic extremes, CO is determined by PBF

Transplantation for single-ventricle patients

Heart transplantation

Single-ventricle physiology remains the most common subset of CHD requiring heart transplantation, with failing Fontan physiology now the predominant indication for orthotopic heart transplantation (OHT) in children and adults with CHD [242]. It is currently predicted that the heterogeneous group of SV patients will ultimately account for 70–80% of OHT in patients with CHD [243]. Due to the scarcity of cardiac donors, particularly for infants, initial surgical or hybrid palliation continues to be the mainstay in the management of functional SV patients. The number of pediatric heart transplants continues to increase each year, with infants <1 year of age accounting for the largest number of transplants and HLHS remaining the most common diagnosis for infants undergoing OHT for CHD [244, 245]. Continued experience and success with ABO-incompatible infant and pediatric cardiac transplantation should assist in enlarging the list of potential donors for patients who require transplantation [246].

A significant percentage of patients with HLHS experience long-term ventricular failure, and some are listed for orthotopic heart transplantation (OHT) even though the initial intention was to pursue the full Fontan palliation pathway. Patients with SV physiology may present for OHT at a wide range of ages and at various palliative stages. Risk factors for heart transplant listing after the Norwood operation include worse RV function, complicated post-surgical course, and diagnosis other than HLHS [247]. The need for transplant before stage II palliation in HLHS patients is associated with poorer waitlist survival, with patients with an mBTTS faring worse than those with an RV-PA shunt. Post-transplant outcomes were unaffected by shunt type [248]. Tweddell et al. identified other risk factors for intermediate-term mortality after transplant in infants with HLHS, including lower socioeconomic status, comorbid genetic syndromes, lower gestational age, and RV function/anatomy [249].

Murtuza et al. reported on 16 OHTs in HLHS patients from a single center from 2000 to 2011 and compared outcomes of these patients with 154 patients who underwent OHT for cardiomyopathy [250]. The 30-day survival was 100% in the HLHS group vs. 98.1% in the 154 patients transplanted for cardiomyopathy, and there were 1- and 5-year Kaplan–Meier survival rates of 100% for HLHS and 87.5% for the cardiomyopathy group ($P = 0.393$). The authors concluded that early and mid-term survival rates are good after OHT in HLHS patients and that transplantation should be a consideration early in HLHS patients with systemic ventricular failure. However, according to the Pediatric Heart Transplant Study database, infants ≤6 months old with HLHS had worse 1-year survival after transplantation than those with cardiomyopathy or other CHD. Infants with HLHS transplanted prior to surgical palliation had a 1-year survival of 79% ($n = 303$), while those who failed surgical palliation had a worsened survival of 70% ($n = 69$) [245].

Refractory Fontan failure may take two forms and ultimately may require OHT. Patients may have Fontan failure as a result of primary ventricular dysfunction; these patients tend to have normal PVR. Fontan failure may also occur with preserved ventricular function but failing Fontan physiology (high Fontan pressures, ascites, PLE and/or PB), and these patients tend to have elevated PVR. A multi-institutional study identified PLE as the reason for OHT in 23% of post-Fontan patients and primary ventricular dysfunction in 31% [251]. Earlier listing for Fontan patients with circulation failure may prevent the associated end-organ comorbidities from developing, which, in turn, may increase the survival post-transplant [252]. Historically, Fontan patients who underwent cardiac transplantation had decreased survival. However, a 2017 Pediatric Heart Transplant Society database study demonstrated that between 2007–2014, 1-year survival for Fontan patients after cardiac transplantation improved to 89%, similar to children with other forms of CHD (92%) [253]. Another study identifying risk factors for post-transplant mortality in Fontan patients found that Model for End-Stage Liver Disease Excluding INR (MELD-XI) scores, history of PLE, and having a VAD at the time of transplant were independent predictors for postoperative mortality [254]. Perioperative management for a failing Fontan should recognize the cardiac depressant effects of induction medications and volatile agents. Anesthetic medications combined with PPV can decrease PBF, ventricular filling, and CO. The anesthesiologist should be prepared to treat significant bleeding, hypotension, and arrhythmias during transplantation [255]. Epinephrine, milrinone, norepinephrine, and vasopressin may be required to wean from CPB, and iNO is frequently used to lower PVR. Bleeding may be robust, and ROTEM and TEG are often used to guide therapy.

Details of cardiac transplantation are discussed in detail in Chapter 32.

Post-Fontan heart-liver transplantation

The decision to perform a heart transplant versus a combined heart liver transplant (CHLT) requires careful consideration. The degree of liver dysfunction or cirrhosis present to prompt CHLT is not known. One study, examining seven patients with Fontan failure who underwent CHLT, used evidence of fibrosis or cirrhosis by imaging or biopsy to determine the need for the liver transplant. The CHLT was performed with the heart implanted first; then, the liver was inspected grossly, followed by choosing whether to proceed with liver transplantation. Patients in this study had 100% 1-year survival [256]. Benefits of CHLT with both organs from the same donor include likely immune protection of the heart by the liver, antigen exposure reduction and decreased chronic rejection, and less coronary graft vasculopathy.

In another study, patients were treated with an *en bloc* CHLT. The decision to perform CHLT over heart transplant alone was based on biopsy and imaging of the liver when possible and after multidisciplinary evaluation to determine liver health. With careful coordination between the cardiac surgery team and the liver transplant team, the heart and great vessels are dissected out while the liver vascular structures are dissected out, and the liver mobilized from the retroperitoneum. The aorta is then cannulated, and cross-clamped and the organs are removed *en bloc*. The implantation begins with the left atrial connection, followed by the IVC. The two teams independently and simultaneously proceed with the implantation. The patient is weaned from CPB when both organs are functioning well, and lastly, the biliary anastomoses are completed. Median blood loss was 6 (2–20) liters, intensive care stay was 19 (5–96) days, and hospital length of stay was 29 (13–197) days. Two patients required an intra-aortic balloon pump, and one required veno-arterial ECMO. All nine patients were alive at 1 year after treatment. Benefits of *en bloc* CHLT include less reperfusion injury to the heart and decreased liver ischemic time compared with sequential CHLT [257].

Non-cardiac surgery and anesthesia for the patient with a single ventricle

Single ventricle patients not infrequently require anesthesia or sedation for procedures other than cardiac surgery. Feeding difficulties are common after the neonatal palliation stage, and many of these patients require gastrostomy tube feeds along with fundoplication. If a procedure is elective, the period after SCPC and before Fontan completion confers a more stable circulation, free from cardiac volume load and delicate balance of Qp: Qs in the shunted SV, and also avoiding Fontan physiology with the harmful effects of PPV and hypovolemia. Fasting time should be minimized, and IV fluids should be optimized to maintain intravascular volume. For patients with Fontan physiology, the ventilatory strategy should include maintaining low pulmonary pressures, minimizing inspiratory pressure, allowing for adequate expiratory time, and avoidance of excessive PEEP. It should be recognized that there is no way for an anesthesiologist to measure a filling pressure percutaneously in a Fontan patient. A study examining complications after non-cardiac procedures in adult Fontan patients found a 15% rate of complications, with baseline cyanosis the only multivariable risk factor identified. The most common complication was hypoxia, and mortality was low at 0.2% [258]. Non-cardiac anesthetics for single-ventricle patients are discussed extensively in Chapter 35.

Summary

Patients with SV physiology undergo staged palliative surgical procedures and also require additional anesthetics for diagnostic procedures, cardiac catheterization, imaging, and non-cardiac surgery. Further surgical or catheter-based interventions are often necessary after Fontan completion. An increasing number of the steadily growing adult population of Fontan patients may ultimately require transplantation. Single-ventricle patients comprise a large proportion of the anesthetic population for the pediatric cardiac anesthesiologist in the modern era at major centers. At Texas Children's Hospital, this proportion was 16.7% of anesthetics for cardiac surgery provided by the Division of Pediatric Cardiovascular Anesthesiology from 2014 to 2021 (data from the Congenital Cardiac Anesthesia Society/Society of Thoracic Surgeons Database provided by David Vener, MD).

Planning anesthetic management for SV patients requires careful assessment to ensure a complete understanding of the typical physiology at each stage of the reconstructive sequence, the specific condition of each patient with respect to that physiology, and the impact that the proposed procedure is likely to have. Optimal results entail good communication and carefully orchestrated interactions between anesthesiologists, surgeons, cardiologists, and intensivists.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

28 Roeleveld PP, Axelrod DM, Klugman D, et al. Hypoplastic left heart syndrome: from fetus to Fontan. Cardiology in the Young 2018;28:1275–88. An excellent, comprehensive modern review of all developments in hypoplastic heart syndrome, literally starting in fetal life, and through the Fontan stage. Emphasizes preoperative risk factors for poor outcomes at each stage, and treatment strategies for improving outcomes.

46 Karamlou T, Overman D, Hill KD, et al. Stage 1 hybrid palliation for hypoplastic left heart syndrome – assessment of contemporary patterns of use: an analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg 2015;149:195–202. In an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database, 13 out of 100 institutions performed >50% of stage I palliations as a hybrid rather than Norwood procedure between 2010 and 2012. With continuing experience and technical modifications, the hybrid procedure may offer the potential for increased survival opportunity with early avoidance of CPB for certain groups including high-risk patients, those awaiting cardiac transplantation, and those with the potential for future biventricular repair.

101 Cholette JM, Willems A, Valentine S, et al. Recommendations on red blood cell transfusion in infants and children with acquired and congenital heart disease from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med 2018;19(9):S137–48. Because PRBC transfusion has been associated with longer duration of mechanical ventilation and ICU stay in stage I palliation patients, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative released recommendations regarding red blood cell transfusion in patients with CHD. One of the key recommendations in this paper state that transfusions should be avoided "solely based upon hemoglobin, if hemoglobin is >9.0 g/dL in infants undergoing staged palliative procedures with stable hemodynamics."

121 Alphonso N, Angelini A, Barron DJ, et al. Guidelines for the management of neonates and infants with hypoplastic left heart syndrome: The European Association for Cardio-Thoracic Surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC) Hypoplastic Left Heart Syndrome Guidelines Task Force. Eur J Cardiothorac Surg 2020;58(3):416–99. An important paper from The European Association for Cardio-Thoracic Surgery and the Association for European Paediatric and Congenital Cardiology that developed a set of guidelines for managing neonates and infants

with HLHS. These guidelines include suggested management for diagnosis, imaging, preoperative assessment, surgical and anesthetic management, and inter-stage monitoring. These recommendations allow practice standardization and identify potential targets for practice improvement at individual institutions.

129 Rao PS. Diagnosis and management of cyanotic congenital heart disease: part I. Indian J Pediatr 2009;76(1):57–70.127. Although different classifications have been proposed for tricuspid atresia (TA,) the most widely accepted schemes are based upon *the relationship of the great arteries* (Type I, II, or III) and *the degree of pulmonary outflow obstruction* (subclassification a, b, or c). This paper nicely summarizes the anatomic classification, incidence, and pathophysiological features of TA.

137 Rao PS. Single ventricle–a comprehensive review. Children 2021;8(6):441. https://doi.org/10.3390/children8060441. A modern, thorough review of all forms of single ventricle hearts and their many anatomic variations. Treatment considerations for catheter or surgical therapy are comprehensively reviewed.

158 Edelson JB, Ravishankar C, Griffis H, et al. A comparison of bidirectional Glenn vs. Hemi-Fontan procedure: an analysis of the single ventricle reconstruction trial public use dataset. Pediatr Cardiol 2020;41:11766–72. Evaluation of over 500 infants in the Single Ventricle Reconstruction Trial dataset were evaluated through 1 year of age, based on the type of superior cavopulmoonary connection performed, bidirectional Glenn vs. Hemi-Fontan. Although CPB times were longer and the use of DHCA more frequent in the Hemi-Fontan group, no difference in transplant-free survival or other important clinical outcomes at 1 year was observed between groups.

178 Herrmann JL, Brown JW. The superior cavopulmonary connection: history and current perspectives. World J for Pediatr Congenit Heart Surg 2019;10(2):216–22. A thorough historical review of the operation, and current outlook for patients undergoing the surgery. A list of risk factors for complications, length of stay, and transplant-free survival has continued to evolve over the past decade. Attrition between the SCPC and Fontan completion for HLHS patients has been reported to be independently associated with moderate or severe tricuspid valve regurgitation and low weight at the time of SCPC.

191 Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart 2016;102:1081–6. A review of the physiology of the Fontan circulation, utilizing visuals of blood traversing these different circulations. Fontan physiology has two significant consequences that affect all Fontan patients to varying degrees: elevated CVP and diminished effective CO. As a result of these, a myriad of end-organ sequelae develop.

192 Gewillig M, Brown SC, Eskynes B. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 2010;10:428–33. An excellent physiological review making the point that post Fontan, the trans-pulmonary gradient. measures the pressure gradient driving blood from the central veins via the Fontan pathway through the lungs and into the common atrium. If pulmonary vascular resistance is elevated, blood flow through the lungs will be impeded, resulting in diminished ventricular filling and decreased cardiac output (CO) *The classic physiologic elements which control CO in a biventricular circulation – heart rate, preload, afterload, and contractility – do not do so in the Fontan circulation*. In a Fontan circulation, except for physiologic extremes such as significant tachycardia, bradycardia, or severe ventricular dysfunction, CO is determined by pulmonary blood flow.

211 Poh CL, d'Udekem Y. Life after surviving Fontan surgery: a meta-analysis of the incidence and predictors of late death. Heart Lung Circ 2018;27:552–9. A comprehensive Fontan registry outcome study analyzing the risk factors and predictors of late death. The quality of life of the post-Fontan patient can be variable, with half of patients experiencing a major adverse event before 14 years of age.

253 Simpson KE, Pruitt E, Kirklin JK, et al. Fontan patient survival after pediatric heart transplantation has improved in the current era. Ann Thorac Surg 2017;103:1315–21. A 2017 Pediatric Heart Transplant Society database study demonstrated that between 2007-2014, 1-year survival for Fontan patients after cardiac transplantation improved to 89%, similar to children with other forms of CHD (92%).

CHAPTER 31
Anesthesia for Miscellaneous Cardiac Lesions

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Introduction

The congenital cardiac anesthesiologist is often faced with caring for patients with lesions and diseases that do not fit neatly into the anatomic and surgical classifications presented elsewhere in this book. This chapter presents vascular rings, coronary artery anomalies, pericardial effusion and tamponade, mitral regurgitation (MR), cardiac tumors, aortic aneurysm and aortopathy, and mediastinal masses. The anatomy, incidence, and natural history are reviewed for all lesions, followed by a discussion of pathophysiology. The surgical approach and outcomes are discussed next, and finally, anesthetic considerations and approaches are presented for each lesion.

Vascular rings

Classification, anatomy, and incidence

Vascular rings have a reported incidence of between 1 in 1,000 births and 1 in 10,000 births [1, 2]. The abnormalities develop from aberrations of the resorption of the six embryonic aortic arches that connect the primitive dorsal and ventral aorta. Normally, the left part of the fourth arch persists as the aortic arch. The persistence of the right part creates a right arch, while the persistence of both parts of the fourth arch creates a double aortic arch. When these arch abnormalities form a ring, partial in some cases, they may produce either esophageal or tracheal compression or obstruction. Chapter 6 presents an extensive discussion of the

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embryology of congenital cardiac and vascular defects. The presence of a complete ring would appear to provide an anatomical explanation for obstruction of the encircled structures, but the relationship between symptoms and the ring and whether it is open or closed is complex and varies with the subgroups of lesions. A comprehensive classification of vascular rings is complex, as an extraordinary number of possible combinations of abnormalities are possible. The International Nomenclature and Database Conferences for Pediatric Cardiac Surgery [3] produced a pragmatic summary noting that describing the particular anatomy of the patient and planning for management based on that description (and symptoms) was more important than creating a "classification." These authors noted that more than 95% of cases associated with symptoms could be described by four categories (Table 31.1) [4].

It is noteworthy that a variant of an otherwise normal left aortic arch is the presence of an aberrant right subclavian arising from the distal arch, which occurs in about 0.5% of normal individuals and is usually asymptomatic. This variant occurs in about a third of babies with trisomy 21. Additional chromosomal variants found in vascular ring patients include 47XXY and 22q11 deletion (DiGeorge syndrome) [5]. Since the increasing use of 3-vessel tracheal view fetal echocardiography after 2004, prenatal detection rates have increased significantly (Figure 31.1) and although there is insufficient data on whether prenatal diagnosis reduces overall morbidity, it does allow for a prospective care plan in those diagnosed [6] (Table 31.2).

Table 31.1 Lurie Children's Hospital, Chicago, vascular ring experience, 1947–2015

Vascular ring	No. of patients
Double aortic arch	155
Right aortic arch/left ligamentum	172
Pulmonary artery sling	46
Total	373

(Source: Backer et al. [4]. Reproduced with permission of Elsevier.)

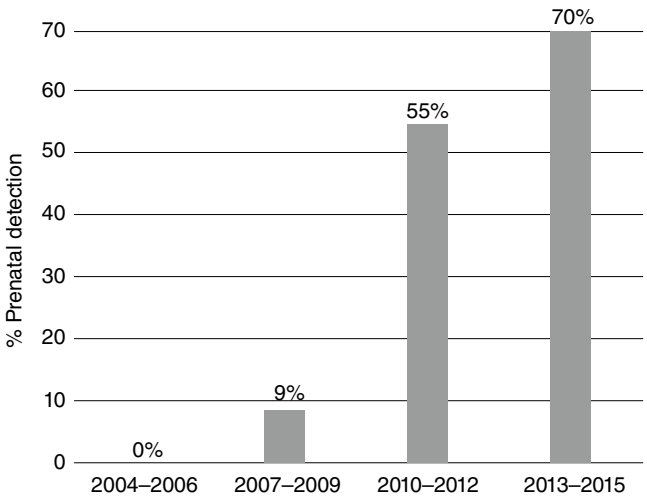


Figure 31.1 Vascular ring prenatal detection rates from 2004–2015 by 3-year intervals. (Source: Evans et al. [6]. Reproduced with permission of SAGE Publications.)

Diagnosis of vascular rings

Definitive diagnosis of vascular rings, once clinical suspicion has been aroused, relies on imaging and, in some cases, endoscopy. Historically barium swallow was a key investigation demonstrating the indentation of the ring on the esophagus. Magnetic resonance imaging (MRI), computed tomographic and CT angiography are now the modalities of choice, allowing three-dimensional (3D) reconstruction of the images and detailed surgical planning [7] (Figure 31.2). CT provides a more precise definition in the tracheobronchial tree and can often be performed without the need for general anesthesia. Greater refinement of operative strategies based on detailed imaging data can lead to improved outcomes for vascular ring patients [8].

Assessment of the fibrous non-vascular parts of the ring is important. Echocardiography can contribute to the diagnosis but is dependent on achieving adequate echocardiographic windows, which may be difficult and is not suitable for assessing the airway [9]. Bronchography and bronchoscopy may be required to define the functional changes, particularly to assess tracheobronchomalacia and to define the extent of tracheobronchial narrowing associated with a pulmonary artery sling.

Vascular rings due to double and right aortic arches: anatomy and natural history

Double and right aortic arches are the result of the persistence of the fourth right embryonic aortic arch and form complete rings around the esophagus and trachea [1]

Table 31.2 Diagnostic data for a 92 patient vascular ring series

	N = 92
Current age years, mean ± SD	9 ± 7
RAA-ALS, n (%)	73 (79)
DAA, n (%)	17 (19)
Pulmonary artery sling, n (%)	2 (2)
Isolated VR, n (%)	75 (82)
RAA-ALS, n	58
DAA, n	15
Pulmonary artery sling, n	2
Dysmorphic syndrome, n (%)	13 (17)
Prenatal detection 2004-2015, n PNDX/n total DX (%)	23/53 (43)
VR with intracardiac CHD, n (%)	17 (18)
RAA-ALS, n	15
DAA, n	2
Dysmorphic syndrome, n (%)	9 (53)
Prenatal detection 2004-2015, n PNDX/n total DX (%)	3/7 (43)
All dysmorphic syndromes and other malformations, n (%)	22 (24)
Down syndrome, n	4
22q11.2 deletion syndrome, n	6
Miscellaneous noncardiac malformations, n	12

Abbreviations: CHD, congenital heart disease; DAA, double aortic arch; DX, diagnosis; PNDX, prenatal diagnosis; RAA-ALS, right aortic arch, aberrant left subclavian artery and patent ductus arteriosus or ligamentum; SD, standard deviation; VR, vascular ring.

(Source: Evans et al. [6]. Reproduced with permission of SAGE Publications.)

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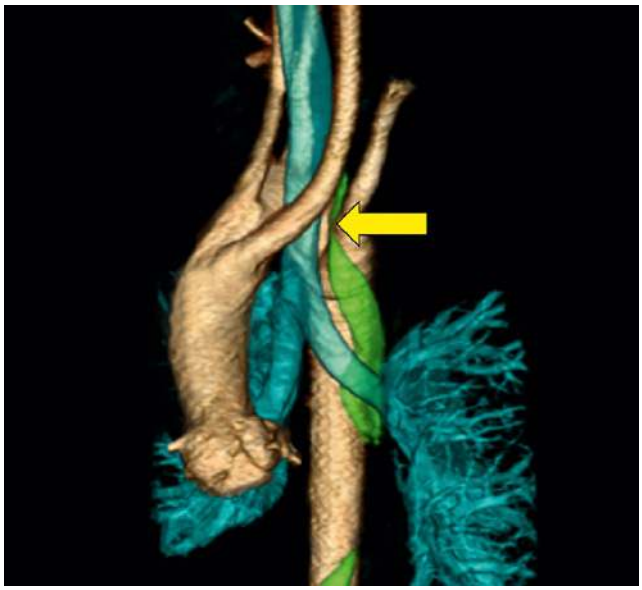


Figure 31.2 Three-dimensional enhanced computed tomography (CT) reconstruction in an 8-year-old patient with right aortic arch, retroesophageal left subclavian artery and Kommerell's Diverticulum. Note severe esophageal compression (yellow arrow) by the Kommerell diverticulum, causing symptoms of "food getting stuck." (Source: Backer [8]. Reproduced with permission of Elsevier.)

(Figure 31.3). They comprise less than 1% of congenital cardiac lesions. The double aortic arch group is commonly described according to whether the left or right arch is dominant or whether they are "balanced," i.e., similar in size. The right aortic arch group may be subclassified by the origin of the left subclavian artery from the right arch. In one-third of right aortic arches, the right arch is a "mirror image" of the normal left arch with the left subclavian branch of the brachiocephalic first branch of the arch, whereas, in two-thirds of cases, the left subclavian is the last major branch of the right arch, passing retro-esophageal to the left upper limb from the right side of the midline. This latter variant may also be associated with dilatation of the origin of the vessel, reflecting the persistence of a segment of fetal aortic arch known as a Kommerell's diverticulum. If this segment is not dealt with at the time of surgical repair, it can cause persistent or recurrent compressive symptoms. Double or right aortic arches with stenosis or coarctation of the aorta are rare. Patients with vascular rings should be echocardiographically assessed for associated cardiac anomalies that occur in approximately 10% of patients [10].

Pathophysiology of vascular rings due to double or right aortic arches

Double and right aortic arches are most commonly present in the first few years of life with respiratory symptoms from tracheal compression. These signs and symptoms include stridor, recurrent respiratory infections, a barking cough, and apnea in infants [4] (Table 31.3). Symptoms of esophageal obstruction are less common, being the primary presentation in about 15% of cases. Esophageal dysfunction may also interact with the respiratory symptoms, because reflux may lead to pulmonary aspiration and episodes of apnea. The development of aspiration pneumonia in the presence of tracheal dysfunction will increase the risk of prolonged pneumonia. The increased work of breathing associated with pneumonia will exaggerate the signs of airway obstruction that may have been absent or subtle when the patient was well. Vascular rings based on double and right aortic arches will encircle the esophagus and trachea. An *in utero* diagnosis by fetal ultrasound does not correlate with the timing and severity of symptoms, and surgery is not indicated unless the patient has symptoms. Children with mild symptoms often have resolution of those symptoms by 4 years of age. Simply observing children who are asymptomatic or mildly symptomatic regardless of aortic arch anatomy is considered a safe approach [11]. However, earlier surgical repair may limit or prevent the development of tracheomalacia, which is not immediately reversed by surgical relief of the obstruction due to the ring. The long-term outcome of vascular ring patients is generally very good. Most commonly these are isolated abnormalities, with approximately 10% of patients also having other significant cardiovascular anomalies. A 2014 study by Razon et al. postulated that although prenatal diagnosis has increased the apparent incidence of disease, the age of surgical repair has decreased. This is perhaps because clinicians caring for these patients now may inherently have a higher index of suspicion that new respiratory or gastrointestinal symptoms are related to the vascular ring. Despite the ability to diagnose prenatally, the authors emphasized that a fetal diagnosis should not be the only indication for surgery [5].

Surgery for right and double aortic arch

Vascular rings are usually repaired through a left thoracotomy. Right thoracotomy or median sternotomy are occasionally used for unusual variants, with median sternotomy being most common when there are other cardiac lesions needing repair. The principle of the surgery is to ensure that the ring is completely divided, which may require division of the ligamentum arteriosum as well as a vascular structure or a fibrous remnant of a vascular structure [1, 12] (Figures 31.4 and 31.5).

If a vascular structure is divided, such as one side of a double aortic arch, it is critical to ensure flow to all parts of the body is maintained. Test clamping and assessment of perfusion to the limbs and head may be required. Some variations of anatomy require reimplantation of blood supply. Such is the case with an aberrant origin of a left subclavian artery from a right aortic arch with a Kommerell's diverticulum – a swelling at the insertion of the left subclavian. The Kommerell's diverticulum can be resected and the left subclavian artery re-implantated onto the left common carotid artery [13] (Figure 31.6). The primary excision of the Kommerell diverticulum is currently the preferred approach since it is now known that its natural history is to steadily enlarge over time [8].

The outcome after surgical repair of vascular rings related to right or double aortic arches is very good with almost no mortality. Relief of obstruction is usually significant. Tracheomalacia may continue to produce postoperative

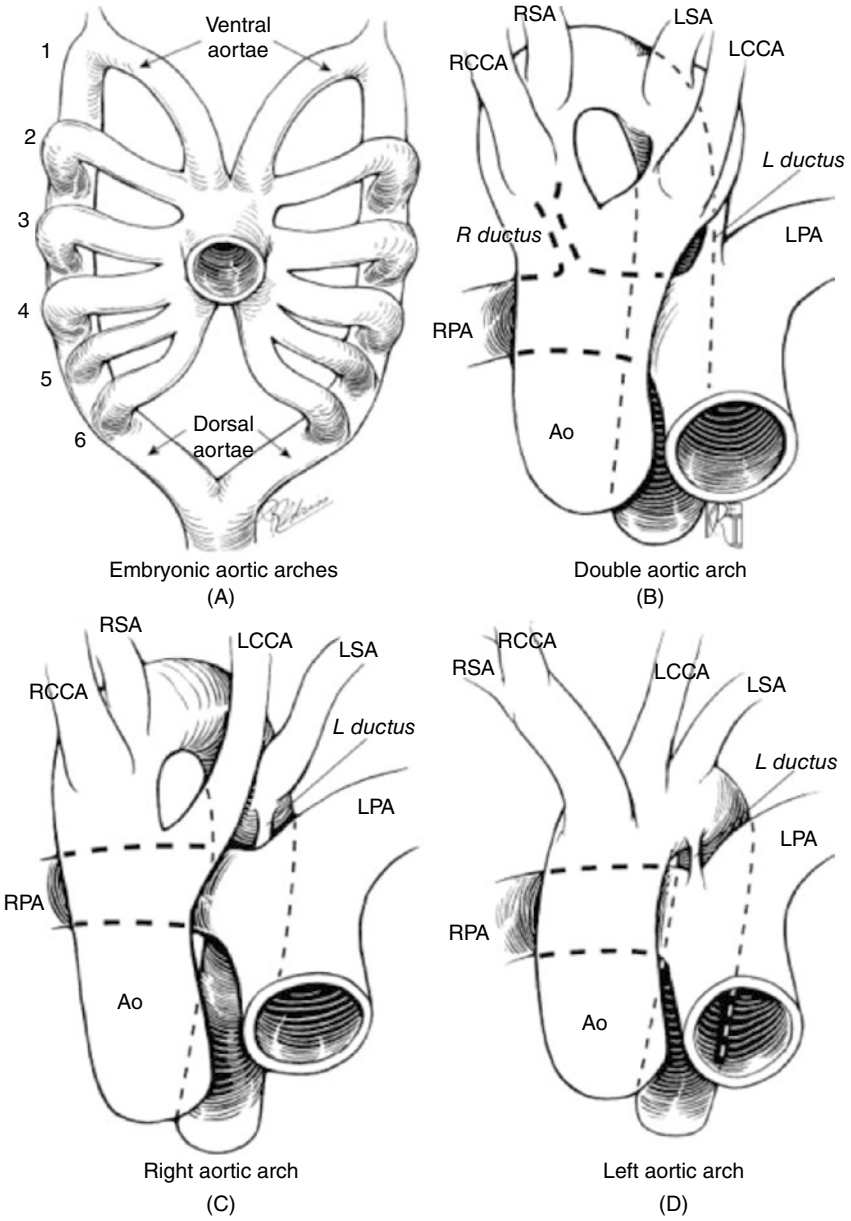


Figure 31.3 Embryonic aortic arches and double aortic arch. (A) Diagram of the embryonic aortic arches. Six pairs of aortic arches originally develop between the dorsal and ventral aorta. The first, second, and fifth arches regress. Preservation or deletion of different segments of the rudimentary arches results in a double aortic arch (B), a right aortic arch (C), or the "normal" left aortic arch (D). Ao, aorta; CCA, common carotid artery; L, left; PA, pulmonary artery; R, right; SA, subclavian artery. Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.

symptoms, but these diminish with the growth of the patient and tissue remodeling [14, 15]. Video-assisted thoracoscopic techniques may be used for these procedures and will influence anesthetic management [16].

Anesthesia for division of vascular rings related to double or right aortic arches

The preoperative assessment should consider the impact that the vascular abnormality has had on the patient, the details of the anatomy and function of the components of the vascular abnormality, the surgical plan, and the requirements for postoperative care. The severity of preoperative obstruction and chronic lung damage from recurrent infections is relevant to the risk of difficulty with oxygenation and ventilation during surgery and in the postoperative period. Chest radiograph findings suggesting chronic lung disease, tachypnea at rest, and rapid desaturation with crying are important indicators of associated lung disease. All other imaging studies, including CT scan, echocardiography, barium swallow, and MRI, should be thoroughly reviewed. The medical and surgical team should decide on the optimal timing of surgical intervention, e.g., can the lung function be further optimized prior to surgery vs. the risk of delaying definitive therapy?

The anesthesiologist and surgeon must have a clear plan regarding the need for lung isolation and discuss monitoring

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Table 31.3 Symptoms leading to clinical presentation in patients with vascular rings[a]

	Double aortic arch (n = 80)[b]	Right aortic arch (n = 78)[b]
Stridor	46 (57%)	18 (23%)
Recurrent upper respiratory tract infections	22 (27%)	18 (23%)
Cough	17 (21%)	8 (10%)
Dysphagia	12 (15%)	12 (15%)
Respiratory distress	8 (10%)	13 (17%)
Ventilator preoperatively	7 (9%)	3 (4%)

Reproduced with permission from Backer et al[5].

[a] More than one symptom occurred in many patients.

[b] Our records did not provide symptoms for the earlier patients in the series.

(Source: Backer et al. [4]. Reproduced with permission of Elsevier.)

requirements if temporary or permanent occlusions of blood vessels are part of the surgical plan. This will influence whether intraoperative access to limbs for circulatory assessment by clinical means, pulse oximetry, intra-arterial pressure monitoring, transcranial Doppler or near-infrared spectroscopy (NIRS) will be required and whether a particular limb is most appropriate for arterial pressure monitoring (not at risk of being lost due to temporary clamping during the procedure).

Intra-arterial pressure monitoring is usually warranted due to the risk of massive hemorrhage, the need for significant intrathoracic retraction during the procedure, and, in some cases, the need to confirm regional perfusion during intraoperative clamping of intrathoracic vessels. Central venous catheterization is usually done for these cases, especially if aortic clamping and suture lines will be required, as pharmacologic control of blood pressure is more safely performed with central venous access. Substantial peripheral venous access should be secured in anticipation of the possible need for rapid resuscitation in the face of surgical blood loss. The procedures usually are associated with minimal blood loss, but preparation should be made for the possibility of massive transfusion.

The tracheal narrowing from vascular rings will not usually prevent an endotracheal tube from being passed through the narrowing. It is rare that positive pressure ventilation and continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) will not be sufficient to allow ventilation during the induction of anesthesia. A single-lumen endotracheal tube is usually adequate for open thoracotomy and often acceptable for thoracoscopic procedures where lung retraction provides good surgical access. If desired, lung isolation may be achieved (see Chapter 23 for a discussion of lung isolation techniques). Rigid or flexible bronchoscopy may be performed pre- and post-procedure in some cases.

Most patients will tolerate early extubation if appropriate analgesia is provided. This will vary with the institution and whether an open or thoracoscopic technique was used. Thoracic epidural analgesia is used in some institutions for thoracotomy for vascular rings. Significant preoperative lung disease or predicted postoperative airway obstruction may require more prolonged intubation and respiratory support.

KEY POINTS: VASCULAR RINGS BASED ON RIGHT OR DOUBLE AORTIC ARCH

- It is important to assess the degree of airway obstruction and whether there is chronic lung disease.
  - Prenatal diagnosis has increased significantly (due to increased ultrasound use) but should not be used as the only indication for surgery.
- Confirm surgical approach (mostly left thoracotomy) and whether regional perfusion (limbs and brain) will need to be assessed intraoperatively (monitoring and arterial line placement).
- Plan postoperative management: early vs. late extubation.
- The tracheomalacia associated with most vascular rings is not immediately cured by relief of the vascular ring.

Innominate artery compression of the trachea: anatomy, diagnosis, and natural history

Innominate artery compression of the trachea is not a true vascular ring [1] (Figure 31.7). Some degree of innominate artery indentation is normal in the first years of life, and the origin of the vessel from the aorta to the left of the trachea is also normal in young children. The normal changes in geometry of this region with growth cause the origin of the innominate artery from the aorta to move to the right of the trachea (not crossing it) and to rotate to the cranial side of the aorta. These changes decrease the degree of tracheal compression caused by the innominate artery as a child grows. Tracheal compression is more likely if the origin of the innominate artery from the aorta is more distal (to the left) and posterior than usual, resulting in anterior compression of the trachea as the vessel passes toward the right side across the front of the trachea. Severity of symptoms and efficacy of medical therapy for acute exacerbations associated with respiratory infection will influence the decision about whether to offer surgery or continue observation and medical therapy, knowing that the natural history of the condition is to improve with growth. Some other congenital abnormalities of this region, including congenital heart disease (CHD), and some patients with repaired esophageal atresia and tracheoesophageal fistula may cause "crowding" of the area, making innominate artery compression of the trachea more likely and perhaps less likely to resolve with time. Dynamic multidetector CT scan (MDCT) is a technique that can provide 2D and 3D reconstructions of thoracic structures. End inspiration and end-expiration images can be used to compare airway patency and can potentially diagnose other anomalies [17]. If extrinsic compression is suspected or identified, MDCT can be vital for surgical planning. For patients with symptomatic tracheobronchial malacia (TBM) the Esophageal and Airway Treatment (EAT) Center at Boston Children's Hospital has found that the dynamic 3-phase bronchoscopy has great diagnostic utility. The first phase occurs while the patient is shallow breathing to reveal resting airway compression, secretion accumulation, and vocal cord motion. The second phase is to induce coughing and Valsalva while

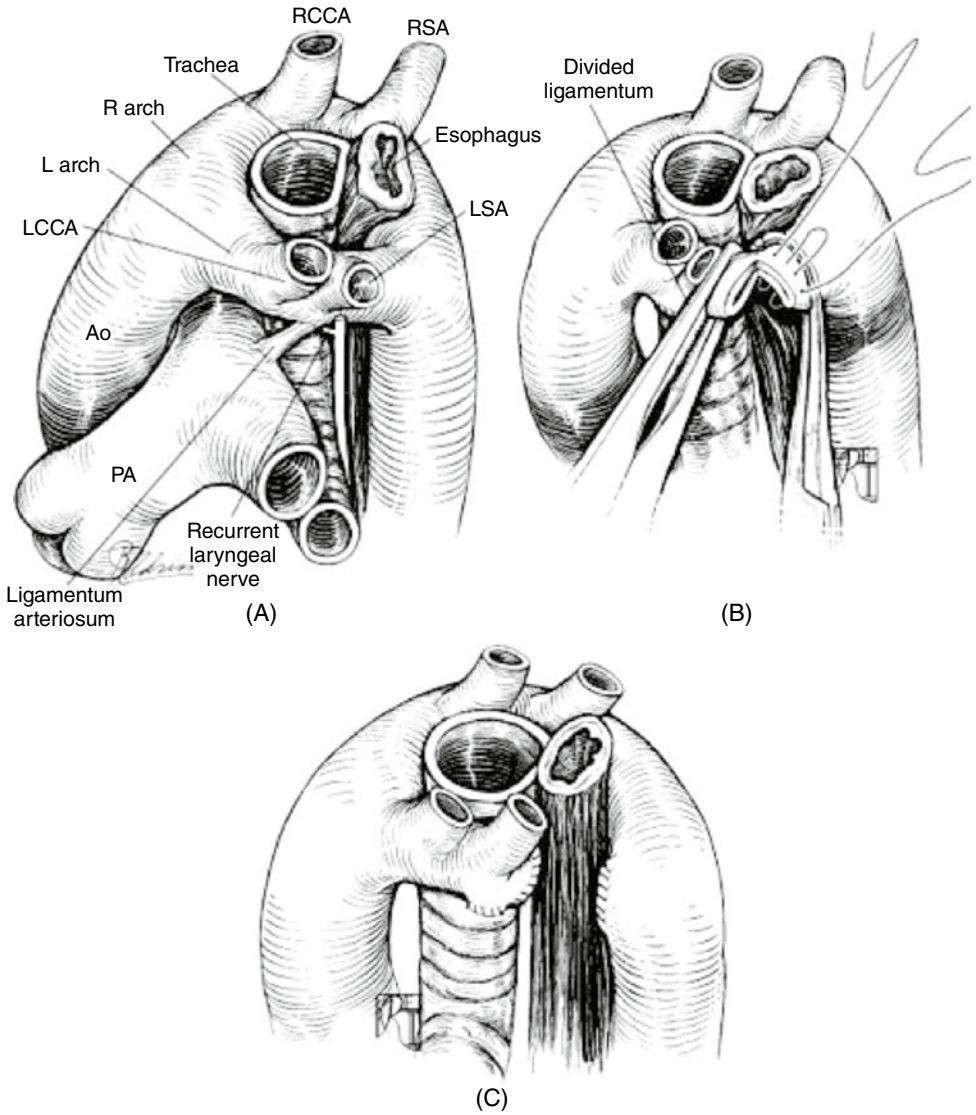


Figure 31.4 Double aortic arch division. (A) Double aortic arch, right arch dominant. (B) Dividing left aortic arch. (C) Arch divided. Ao, aorta; CA, carotid artery; L, left; LCCA, RCCA, left, right carotid artery; PA, pulmonary artery; R, right; SA, subclavian artery. (Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

observing for maximum dynamic collapse in the entire airway. The third phase is to distend the airway with 30–60 cm H20 pressure in order to reveal lesions that may not have been previously recognized such as fistulas, diverticuli, and aberrant bronchi. Careful documentation of the area of tracheal involvement can also aid in the correct classification and subsequent response to treatment [17].

Pathophysiology of innominate artery compression of the trachea

Symptomatic innominate artery compression syndrome produces a localized narrowing of the trachea, often with a localized segment of tracheomalacia. Symptoms typically do not appear until there is more than 50% obstruction of the trachea. The condition presents with stridor and airway obstruction, often with an abnormal harsh cough relating to the associated tracheomalacia. Innominate artery compression of the trachea may underlie some presentations of recurrent croup. Because there is some degree of tracheal impression from the innominate artery in normal young children, it is important not to overdiagnose this condition with the risk of significant surgical intervention offered inappropriately.

Surgery for innominate artery compression of the trachea

Surgery for this condition is not commonly indicated except for significantly symptomatic patients where conservative therapy is deemed inappropriate. Most of the procedures are done through a left thoracotomy, but sternotomy and right thoracotomy have been used for vascular suspension procedures. Surgery can involve aortopexy of the innominate artery and aorta anterior to the sternum, which has a modest risk of recurrence, or reimplantation of the

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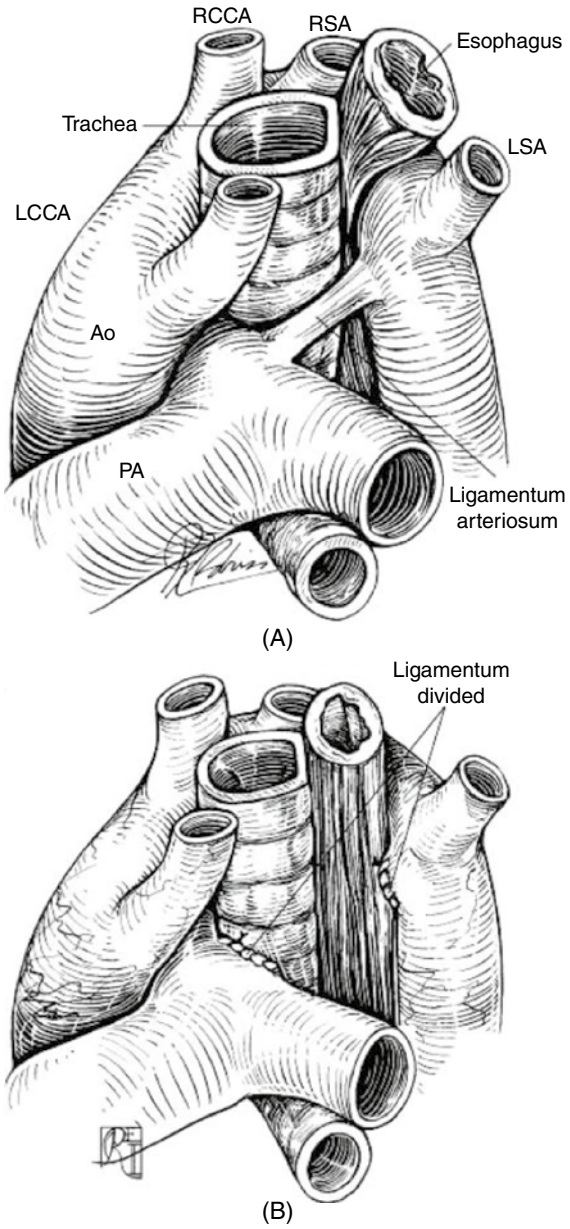


Figure 31.5 Right aortic arch – division and oversewing (B) of ligamentum arteriosum (A). Ao, aorta; CCA, common carotid artery; L, left; MPA, main pulmonary artery; R, right; SA, subclavian artery.) (Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

innominate artery so that its origin from the aorta is to the right of the trachea and from the cephalad aspect of the aorta [1] (Figure 31.8). This is a more complex procedure with a greater risk of complications, but it definitively eliminates the innominate artery as a cause of tracheal compression. Anterior and/or posterior tracheopexy have been described as a novel management technique for TBM when aortopexy alone was unable to address tracheal cartilage abnormalities or membranous luminal intrusion. Anterior tracheopexy anchors the trachea to the sternum similar to aortopexy and posterior anchors the trachea to the anterior longitudinal spinal ligament. Both techniques are done with direct bronchoscopic guidance to ensure the sutures remain extraluminal and avoid excess tension in the trachea [17]. either procedure, residual tracheomalacia may cause ongoing symptoms.

Anesthesia for the repair of innominate artery compression of the trachea

The preoperative general assessment is similar to that described for vascular rings. The conduct of anesthesia is simplified if aortopexy of the innominate/aorta is the surgical technique because the risk of major intraoperative complications or the need for vascular clamping is minimal. Reimplantation of the innominate artery will involve more specific and intense intraoperative monitoring, which will include consideration of the aortic surgery and temporary occlusion of the innominate artery. For continuous arterial pressure monitoring, an arterial line can be placed in the left radial artery. Information about the adequacy of collateral perfusion during clamping of the innominate can be gained by placing an arterial line in the right radial artery. Previous case series have not noted stroke as a significant risk during temporary clamping of the innominate artery, but monitoring of cerebral perfusion, e.g., with NIRS, may be warranted to confirm minimal risk of ischemic stroke due to poor perfusion relating to clamping. Anticoagulation (normally 100 units/kg heparin; target activated clotting time 180–200 seconds) is used to minimize the risk of embolus or thrombosis related to innominate artery reimplantation. Bronchoscopy, either rigid or flexible, is frequently performed pre- and post-procedure to assess results of surgery or in the case of tracheopexy may actually be needed to guide the surgical procedure. Postoperative care will be predicated on similar principles to vascular ring procedures.

KEY POINTS: INNOMINATE ARTERY COMPRESSION SYNDROME

- Some innominate artery compression of the trachea is normal.
- Natural history is for obstruction to decrease with growth, so conservative management is often justified.
- Simple suspension aortopexy is usually adequate for cases that require surgery and will "buy time" for growth but more complex procedures such as tracheopexy may be needed.
- Formal reimplantation of the innominate artery is more definitive surgery but far more complex a procedure with a number of potential complications.

Pulmonary artery sling with tracheal stenosis: anatomy and natural history

Pulmonary artery sling results from an aberrant course of the left pulmonary artery around the trachea, which may restrict the space in which the trachea forms [1] (Figure 31.9). The left pulmonary artery arises from the posterior surface of the

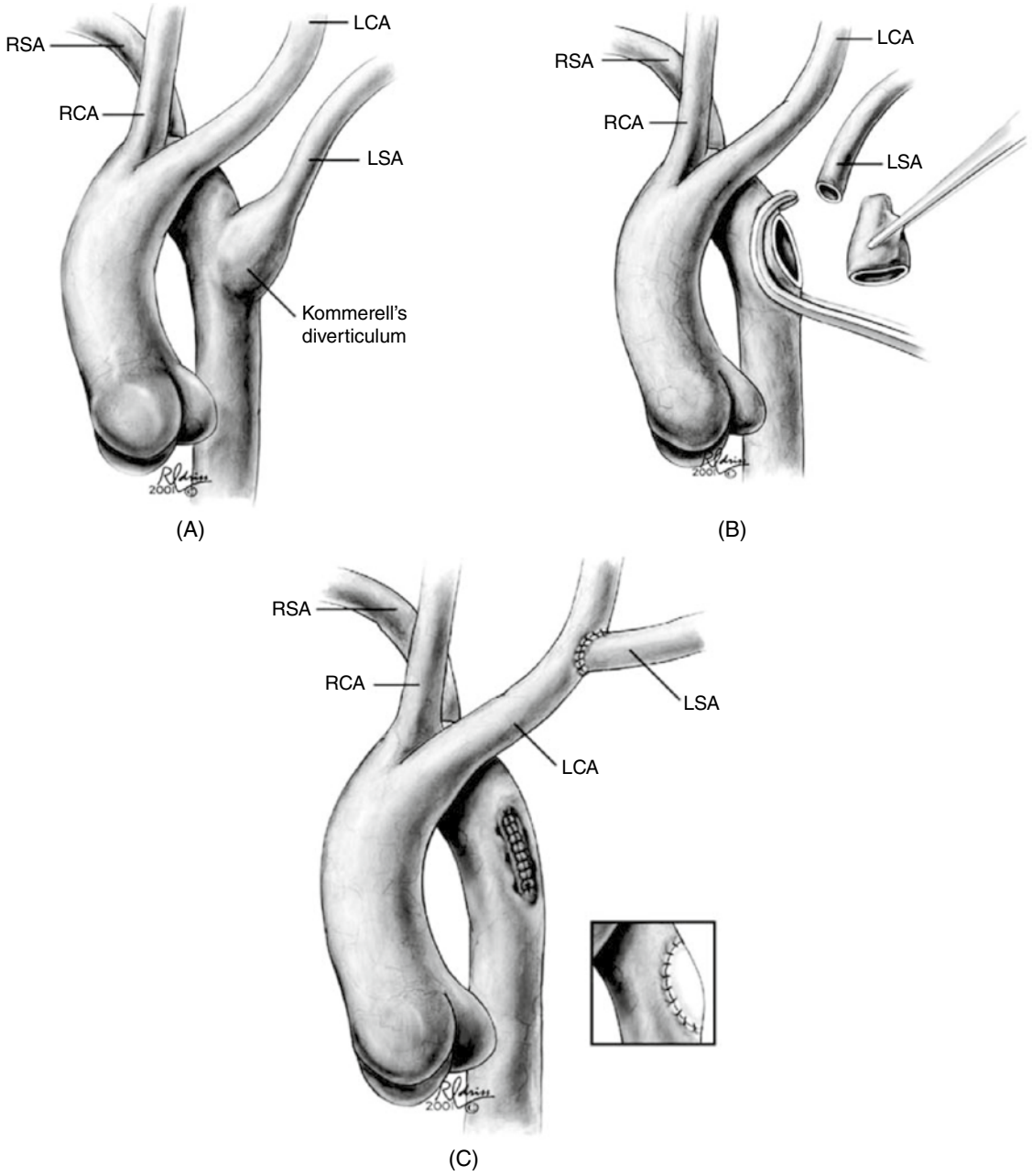


Figure 31.6 Resection of Kommerell's diverticulum. (A) Typical anatomy of a patient with a right aortic arch, retroesophageal left subclavian artery, and large Kommerell's diverticulum. LCA/RCA, left/right carotid artery; LSA/RSA, left/right subclavian artery. (B) There is a vascular clamp partially occluding the descending thoracic aorta at the origin of the Kommerell's diverticulum, which has been completely resected. (C) The completed repair. The orifice where the Kommerell's diverticulum was resected is usually closed primarily or patched if necessary. The left subclavian artery has been implanted into the side of the left common carotid artery. (Source: Backer et al. [13]. Reproduced with permission of Elsevier.)

right pulmonary artery and passes over the superior surface of the right main bronchus then posterior to the trachea and anterior to the esophagus to the left lung. The most important factor that determines prognosis is the association of this lesion with segmental narrowing of the trachea, and sometimes bronchi, with complete cartilaginous rings in the affected segment, the so-called "rat-tail trachea." A long segment of narrowing worsens the prognosis. Curiously, these patients frequently do not present for some months after birth, often with airway obstruction associated with an apparently minor respiratory infection. Recent advances in tracheal reconstruction have been associated with an improved outcome. Imaging studies are crucial for accurate diagnosis. Echocardiography may provide initial diagnosis, but anatomic detail is better provided by CT or MRI; cardiac catheterization is rarely indicated for this problem.

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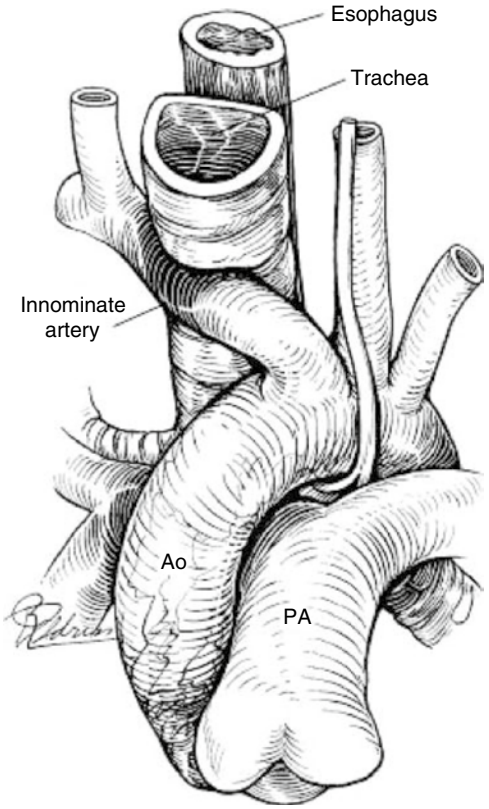


Figure 31.7 Innominate artery compression of anterior trachea. Ao, aorta; PA, pulmonary artery. (Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

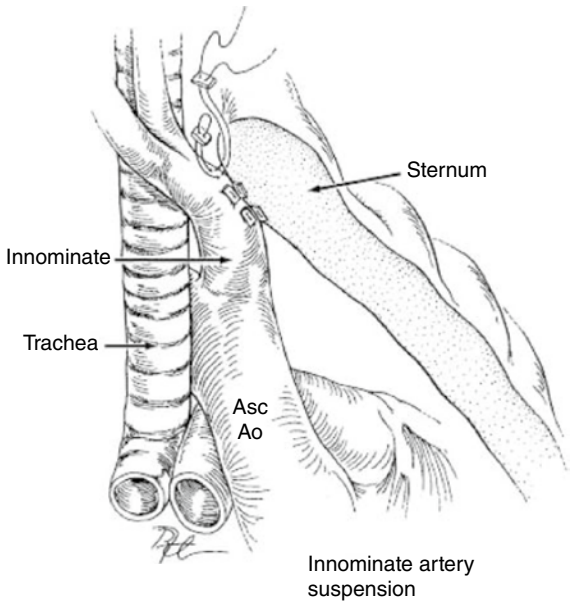


Figure 31.8 Innominate artery suspension. Exposure is through a right submammary thoracotomy. Fixing the adventitia of the innominate artery to the posterior table of the sternum with pledgeted sutures pulls the innominate artery anteriorly and actively pulls the tracheal wall forward and opens it. Asc Ao, ascending aorta. (Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

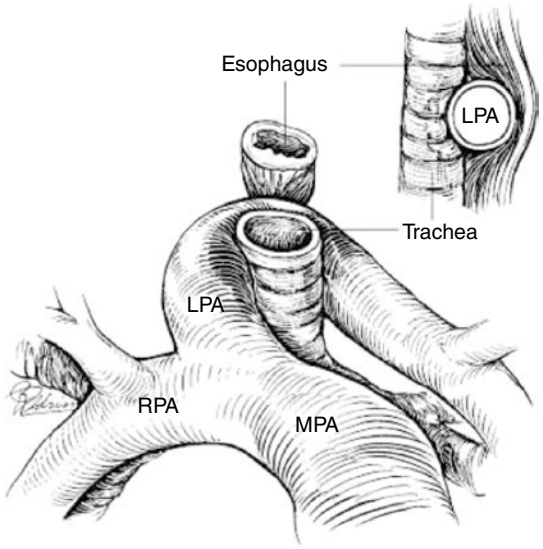


Figure 31.9 Pulmonary artery sling. L, left; M, main; PA, pulmonary artery; R, right. Inset: left lateral view of anterior compression of the esophagus and posterior compression of the trachea. (Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

Pulmonary artery sling with tracheal stenosis: pathophysiology

Pulmonary artery sling pathophysiology is focused on the severity and length of the associated tracheobronchial narrowing. It is not clear whether the usual delay in presentation until some months of life represents primarily a failure of further growth of airway diameter or an increase in ventilatory requirements as the child grows. A common clinical scenario is an apparently minor respiratory infection in the middle of the first year of life, leading to obvious signs of increased work of breathing relating to respiratory obstruction with slow or incomplete resolution of the illness. Distinguishing this from the far more common bronchiolitis and laryngotracheobronchitis infections in children with underlying normal airways is difficult at the primary presentation. The severity of obstruction, failure of resolution, and recurrent presentation are the usual triggers for further investigation and diagnosis of the patient with pulmonary artery sling. Huang and colleagues recommend tracheoplasty surgery if the tracheal width is less than 3 mm [18]. An Australian retrospective study of 33 PA sling patients by Yong and colleagues analyzing cases showed that long-term outcomes and survival are often worsened by the need for tracheal surgery [19] (Figure 31.10). Early mortality was clearly increased in those requiring surgery on the trachea. A review of pulmonary function testing several years after tracheal surgery demonstrated that a non-reversable obstructive pattern was often demonstrated on pulmonary function testing suggesting the need for long-term respiratory assessment of these patients.

Surgery for pulmonary artery sling with tracheal narrowing

The long-term outcome of the surgical intervention for these patients depends on the tracheal reconstruction. The surgery

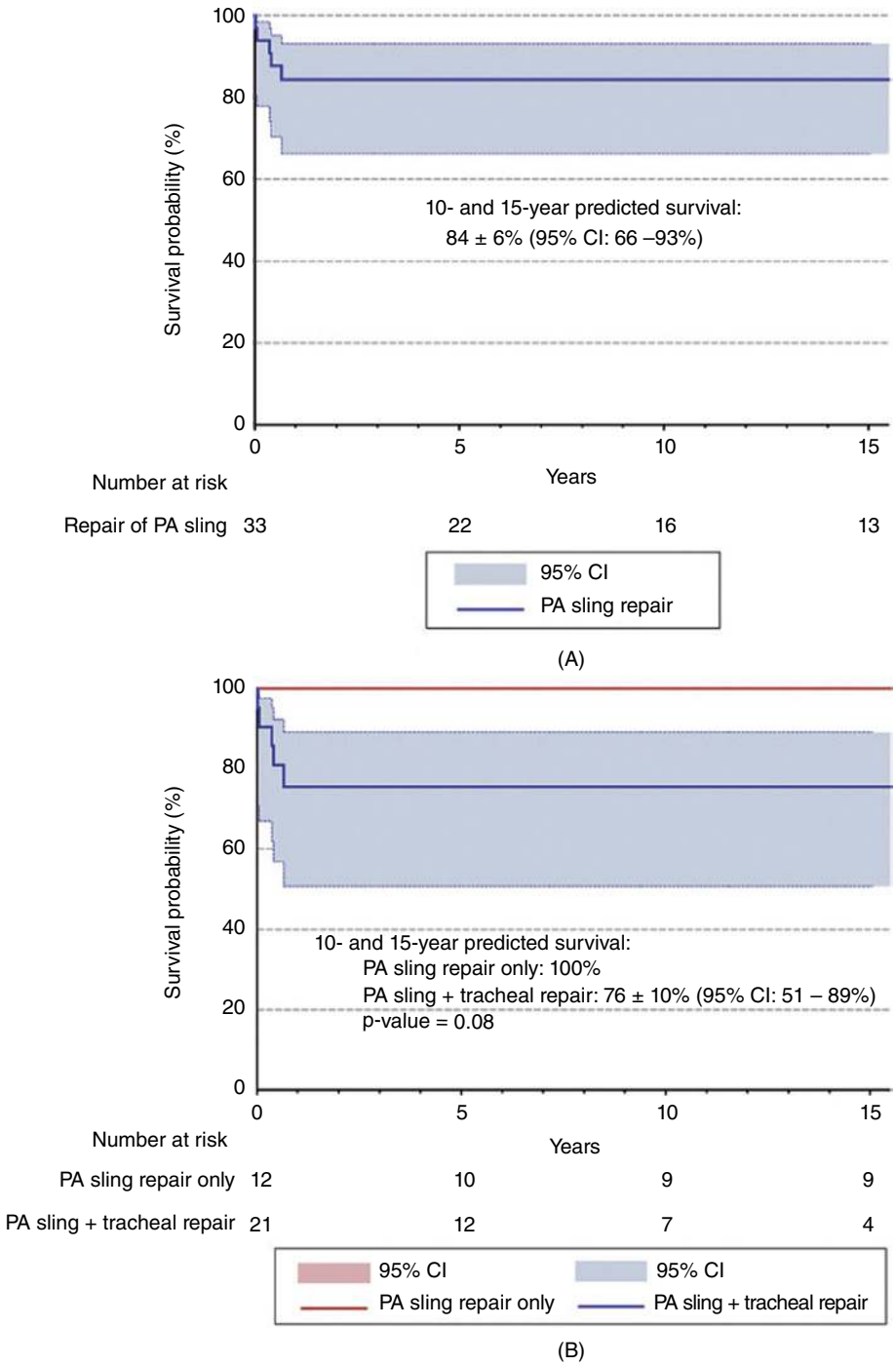


Figure 31.10 Kaplan-Meier curve showing probability of survival in (A) all patients who had pulmonary artery (PA) sling repair and (B) patients who had PA sling repair only compared to patients who had both PA sling and tracheal repair. CI, confidenc interval. (Source: ReproducedYong et al. [19]. Reproduced with permission of Springer Nature.)

is done through a sternotomy, on cardiopulmonary bypass (CPB). The aberrant left pulmonary artery can be dealt with at the time of reconstruction of the trachea, most commonly by dividing and reimplanting it, to mimic the normal takeoff from the main pulmonary artery, but alternative methods to relocate the vessel in relation to the reconstructed trachea have been used.

For patients with a short segment of tracheal stenosis, resection of the stenosis, mobilization of the trachea, and direct anastomosis may be sufficient and relatively straightforward surgery [1] (Figure 31.11). For patients with a longer segment of narrow trachea with complete rings, the long-term problem with tracheal reconstruction has been to achieve both continuing adequate airway patency and a functional

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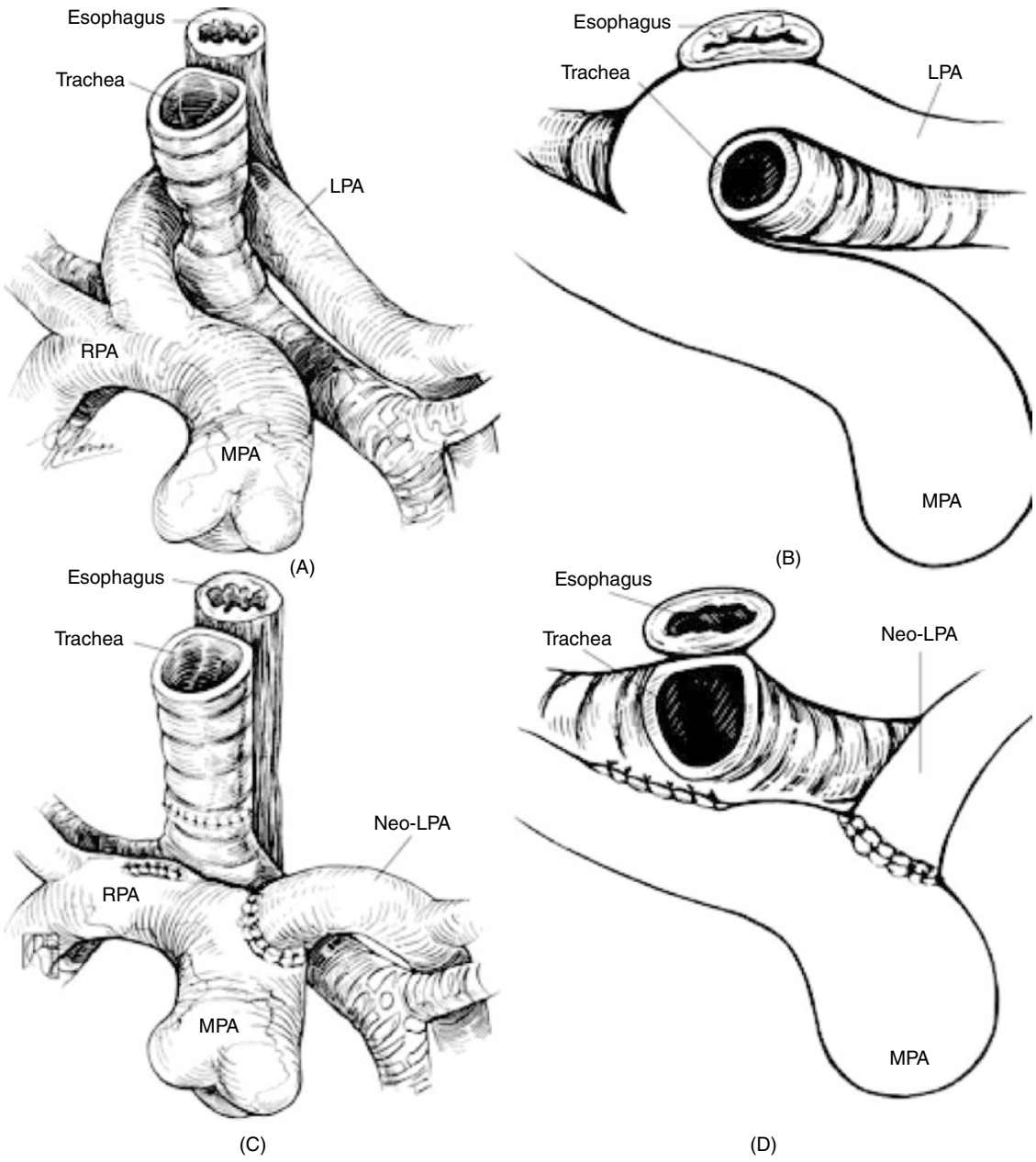


Figure 31.11 Illustration of operative technique for pulmonary artery sling repair with tracheal resection (performed with cardiopulmonary bypass). (A) Left pulmonary artery (LPA) encircles and compresses the distal area of the trachea and right main-stem bronchus. (B) Relationship of the LPA to the trachea and esophagus. (C) Repair is by transecting the LPA at its origin from the right pulmonary artery (RPA) and anastomosing the LPA to the main pulmonary artery (MPA) at a site that approximates the usual anatomic configuration. The tracheal stenosis has also been resected, and an end-to-end tracheal anastomosis is shown. (D) Postoperative relationship of neo-LPA to MPA anastomosis showing the relatively long distance from the original LPA takeoff from the RPA. (Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

tracheal epithelium. The airway patency must be throughout the respiratory cycle, which requires a degree of rigidity to resist collapse in expiration. For long segment reconstruction, the slide tracheoplasty has become the preferred surgical approach. Tracheal surgery is technically demanding and should ideally be performed in centers that do large numbers of cases [20]. Alternatives, such as simple patches (e.g., with pericardium), will usually be associated with tracheomalacia in the long term. Scarring and granulation formation and the lack of cilial function will often complicate stented patches, whether stented by external, surgically placed cartilage grafts or internal stents, similar to those used for vascular stenting. There is currently no data to support stenting as a primary approach for tracheal stenosis patients but they are often used as a bridge to surgical therapy [20]. The most commonly cited complications of currently available intraluminal stents are stent migration, degradation and fragmentation [21]. A systematic review of 26 studies of intraluminal stents showed an

overall complication rate of 21.7% (8.7% stent fragment foreign body and 4.3% each for stent migration, local stenosis, and granulation tissue) A more complex style of self-expanding helical stent is under preclinical investigation. It is made of nitinol, a nickel-titanium alloy, designed specifically to minimize foreign-body reaction, preserve mucociliary transport, and facilitate atraumatic removal [22, 23]. External custom 3-D printed bio-reabsorbable tracheal splints are also under clinical investigation [18], and may allow time for tracheal growth but require an more complex open surgical procedure [18, 24]. Alternative sources of tissue, such as laboratory-based tissue engineering or donor tissue, are possible, but slide tracheoplasty has the potential to provide airway patency, with a non-collapsing wall and normal functioning respiratory epithelial mucosa.

Slide tracheoplasty is a solution for many longer segment narrowings which optimizes the use of native tissues to reconstruct the trachea and potentially proximal bronchi [25] (Figure 31.12). The technique involves an oblique division of the trachea, with the distal and proximal ends of the incision continued on the proximal trachea and distally, and potentially along a bronchus if there is bronchial involvement. The trachea is mobilized so that the oblique end of the proximal trachea can slide into the apex of the distal incision, and the oblique end of the distal trachea can slide into the apex of the proximal incision. This achieves expansion of the lumen, with essentially normal tracheal tissue and mucosa forming the reconstructed trachea. The long oblique anastomosis is less likely to stricture than a circular anastomosis. The slide maneuver shortens the trachea. Independent of symptom severity, DLR (diameter/length ratio) is defined as the ratio of the narrowest diameter divided by the stenotic segment length. DLR has been reported by Hong and colleagues as a potentially reliable indication for surgery in patients with congenital tracheal stenosis with pulmonary artery sling [26]. According to Harada and colleagues, a DLR of less than 5.9 may be a reliable indicator for slide tracheoplasty in addition to vascular repair [27].

Patients with a long segment of tracheobronchial narrowing in association with a pulmonary artery sling may well benefit from a multidisciplinary assessment. These patients should be managed at an appropriate referral center. According to an analysis by Chen and colleagues of 23 children between 2003 and 2018, slide tracheoplasty can be performed for up to two thirds of the length of the trachea. Beyond this length, tension-relieving maneuvers may be required to prevent complications such as anastomotic breakdown, recurrent granulation tissue, and a narrowed lumen [28]. It is desirable that cardiac surgery, cardiology, thoracic and otolaryngological surgery, anesthesia, pulmonary medicine, intensive care, and medical imaging and intervention should all participate and collaborate in planning the management of these patients.

Anesthesia for the repair of pulmonary artery sling and tracheal stenosis

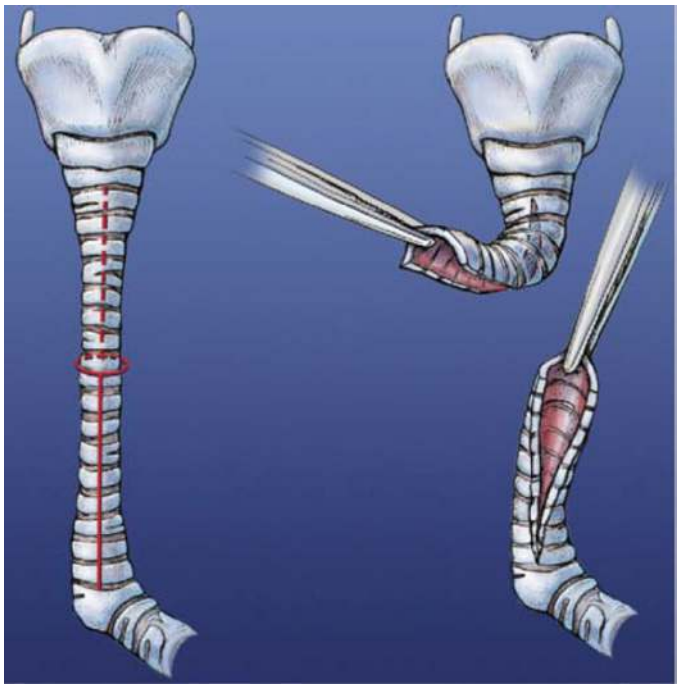
The anesthesia assessment of these patients is particularly focused on the impact and extent of the associated tracheal stenosis. The indications and timing of surgery are entirely driven by symptoms related to the tracheal obstruction. The spectrum of these patients' conditions may well range from a minimally symptomatic baby who is requiring no current intervention to a patient in a perilous situation with maximum intensive care support, with complex ventilator requirements and potentially requiring extracorporeal oxygenation or carbon dioxide clearance. Positive pressure ventilation in these patients is difficult to optimize and assessing flow volume loops created by different ventilator strategies can be helpful. Common strategies include permissive hypercapnea, attention to adequate expiratory time to minimize hyperinflation which limits ventilation, and continuous positive pressure to maintain airway patency.

Anesthesia is similar to other procedures requiring CPB. Passing an endotracheal tube through the larynx is initially as for a normal patient. The difference is that a tube that is appropriate for the upper trachea will not pass through the narrow segment. No attempt should be made to advance the endotracheal tube through the narrowing. Bronchoscopic assistance may be utilized or the tube can be gently advanced through the larynx until resistance is felt and minimally withdrawn from that point. The narrow segment of the trachea can easily be blocked by blood, swelling, or secretions associated with trauma to the mucosa, with potentially catastrophic results. Avoiding these complications by minimizing airway trauma is a primary aim. If required, suctioning may require a fine catheter and lubrication to clear secretions from the narrow segment. Suctioning may be necessary for adequate ventilation but runs the risk of traumatizing the mucosa. Suctioning may be life-saving if secretions or blood occlude the narrow segment. High inspiratory pressures may be required to inflate the lungs, as the narrow segment may have a very high resistance to flow. For this reason, consideration should be given to ensuring that the largest appropriate tube is placed above the narrowing to minimize the risk of an excessive leak at high ventilator pressures or inability to generate adequate pressure. If there is sufficient length of trachea above the narrowing, a tube with a cuff, particularly one with the minimum distance between the cuff and the tip of the endotracheal tube, may be appropriate. Bronchoscopic confirmation and guidance of placement should be considered.

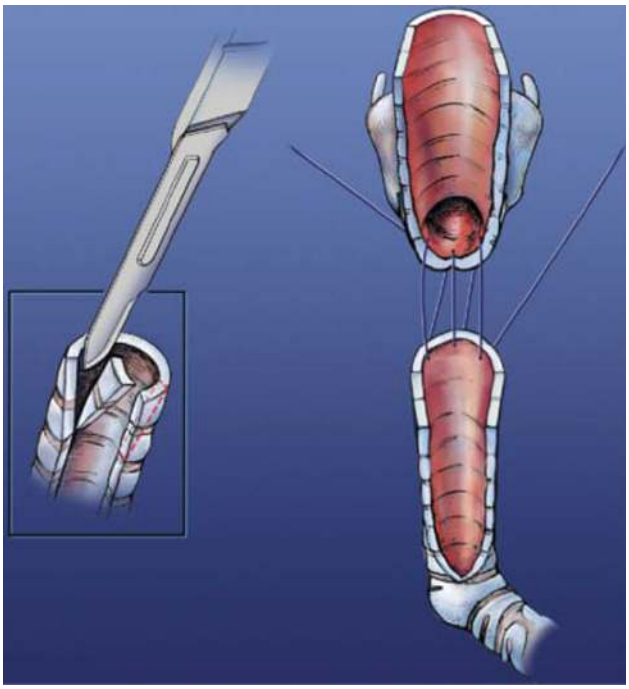
The mobilization and slide maneuver associated with slide tracheoplasty will tend to draw the trachea down into the chest, meaning that the distance between the larynx and the tip of the endotracheal tube placed at the beginning of the procedure will decrease. This should be assessed, and the endotracheal tube confirmed to be in a good position before transporting the patient to the intensive care unit.

With adequate surgical relief of tracheal obstruction and air-tight closure of the tracheal (or tracheobronchial) anastomosis, the patient should tolerate positive pressure ventilation postoperatively and the endotracheal tube can be left above the anastomosis. Early extubation is usually avoided, as postoperative swelling over the next few days may still be associated with a restricted airway. Fiberoptic bronchoscopic examination via the endotracheal tube can guide decision-making about airway management, as well as provide controlled airway suctioning and assist with deciding the best position for the endotracheal tube during the postoperative course. Although a relatively early return to spontaneous ventilation may minimize the need for positive pressure

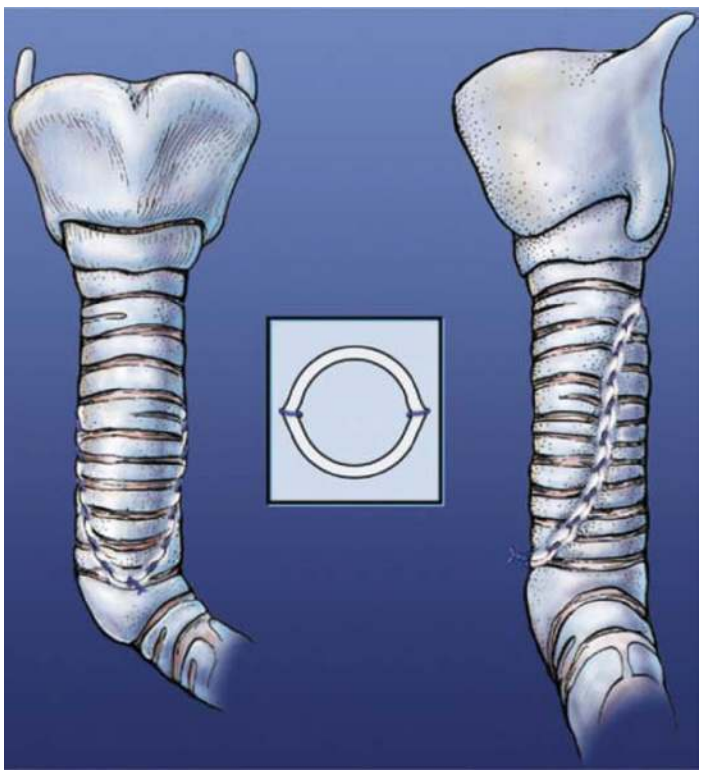
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(A)



(B)



(C)

Figure 31.12 Slide tracheoplasty. (A) The trachea is transected in the midportion of the tracheal stenosis. This site is determined by either external examination or internal bronchoscopic findings. The inferior portion of the trachea is incised anteriorly and the superior portion of the trachea is incised posteriorly. (B) The ends of the trachea are beveled as shown in the small inset. The suture line is started superiorly (parachute technique) and finished inferiorly just above the carina. (C) Completed slide tracheoplasty. (Source: Backer et al. [12]. Reproduced with permission of Elsevier.)

ventilation, decreasing the risk of air leak, coughing or straining on the endotracheal tube, perhaps related to decreased sedation to allow spontaneous ventilation, could be associated with a greater risk of air leak. The management plan will require repeated assessment if clinical circumstances change.

Box 31.1 Summarizes the surgical approach to vascular rings and slings [1].

KEY POINTS: PULMONARY ARTERY SLING

- The outcome is mostly determined by the degree of tracheobronchial obstruction.
- The affected segment of the tracheobronchial tree has complete cartilage rings.
- Repair on CPB includes dealing with the pulmonary artery sling but repair of tracheobronchial obstruction is crucial.
- Excision of the narrow segment may be possible for short segments, but slide tracheoplasty is the usual technique for longer segments and long-term outcomes are favorable with excellent late survival
  - Tracheopexy may help treat severe tracheobronchomalacia
  - DLR may be a reliable indicator for surgical intervention
  - Tracheal stenting and splinting are not currently first-line treatment options but improvements in these technologies are currently under investigation.

Box 31.1: Surgical management of vascular rings

Double aortic arch
1. Left thoracotomy (muscle-sparing – fourth interspace)
2. Divide lesser of two arches at insertion with descending aorta
3. Preserve blood flow to carotid/radial arteries
4. Ligate and divide ligamentum arteriosum
5. Leave pleura open

Right aortic arch/left ligamentum
1. Left thoracotomy (muscle-sparing – fourth interspace)
2. Ligate and divide ligamentum arteriosum
3. Resect Kommerell's diverticulum (if present) and transfer the left subclavian artery to the left carotid artery
4. Leave pleura open

Innominate artery compression syndrome
1. Right anterolateral thoracotomy (third interspace)
2. Resect right lobe of thymus
3. Suspend innominate artery to posterior sternum
4. Postoperative bronchoscopy

Pulmonary artery sling
1. Median sternotomy/extracorporeal circulation
2. Ligate/divide left pulmonary artery (PA)
3. Implant left PA into main PA anterior to the trachea
4. Slide tracheoplasty for associated tracheal rings

(Source: Backer & Mavroudis [1]. Reproduced with permission of John Wiley & Sons.)

Anomalies of the coronary arteries

There is a wide anatomic variation of the coronary arteries. There are a number of common variants which are accepted as normal but which may have significance if the disease of the coronaries develops (e.g., proximal atheroma in a single coronary artery which gives rise to left and right coronary arteries) or surgery of the region is required (where intramural or unusually placed vessels may be more likely to be injured). The physiological function of the coronary arteries and the heart is usually normal in these variations.

The focus of this section is congenital anomalies of the coronary arteries. Acquired abnormalities are also important in childhood. These include infective causes, of which Kawasaki disease is the most prominent, iatrogenic causes arising from surgery or invasive cardiological procedures, and the development of abnormalities in relation to other lesions, such as the coronary perfusion issues that can be associated with supravalvular aortic stenosis.

The Congenital Heart Surgery Nomenclature and Database Project provided an excellent classification and review of the significance of anomalies of the coronary arteries [29]. The major types of coronary anomalies are divided into the following seven groups:

1. Anomalous pulmonary origins of the coronaries
2. Anomalous aortic origins of the coronaries
3. Congenital atresia of the left main coronary artery
4. Coronary arteriovenous fistulas
5. Coronary artery bridging
6. Coronary artery aneurysms
7. Coronary stenosis.

Coronary anomalies are a diverse group of disorders with varying clinical manifestations for which history and physical exam are extremely unreliable in diagnosing these rare conditions which rarely cause symptoms at rest. They are the second most common cause of sudden cardiac death in young competitive athletes [30]. A similarly high incidence of coronary anomalies has also been seen at autopsy of young military recruits who died suddenly [31]. A 2018 MRI screening study by Angelini and colleagues of a general population of 5,000 adolescents participating in school sports revealed a 1.3% incidence (70 cases) of high-risk cardiovascular disease including 23 study members with AOCOS anomalies (anomalous origin of a coronary artery from the opposite sinus) [32] (Table 31.4). Left sided AOCOS with an intramural course (L-AOCOS-IM) constitutes the most serious group of all LCA anomalies [34]. During strenuous exercise the proximal intramural course predisposes to lateral compression and phasic narrowing during systole potentially leading to ischemia. An intra-arterial course between the great vessels has also been found to be problematic and is often difficult to confirm with imaging [35]. Screening for these abnormalities in children has become a recent topic of focus but no clear guidelines have yet been established.

Supravalvular aortic stenosis is also clinically important and associated with sudden death, sometimes in association with apparently stable anesthesia, and the complex mechanisms, which may be both structural and dynamic. The development of abnormalities of coronary perfusion in this condition is discussed.

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Table 31.4 Prevalence of potentially high-risk cardiovascular conditions

	Total cohort			Ages 11–14 years		Ages 15–18 years	
	***N* = 5169**	**Frequency (%)**	**95% CI**	***n* = 4310**	**Frequency (%)**	***n* = 859**	**Frequency (%)**
Total hr-CVC	76	1.47	1.16–1.84	62	1.44	14	1.63
hr-ACAOS	23	0.44	0.28–0.67	20	0.46	3	0.35
L-ACAOS-IM	6	0.12	0.04–0.25	6	0.14	0	0
RSV	2	0.04	0.01–0.10				
NC	2	0.04	0.01–0.10				
HO	2	0.04	0.01–0.10				
R-ACAOS	17	0.33	0.19–0.53	14	0.32	3	0.35
hr-CMP	14	0.27	0.15–0.45	6	0.14	8	0.93
DCM	11	0.21	0.11–0.38	5	0.12	6	0.70
HCM	3	0.06	0.01–0.17	1	0.02	2	0.23
ECG hr-CVC	39	0.75	0.54–1.03	36	0.84	3	0.35
Brugada	1	0.02	0.00–0.11	0	0	1	0.12
WPW	4	0.08	0.02–0.20	4	0.09	0	0
QTc ≥ 470 ms	34	0.66	0.46–0.92	32	0.74	2	0.23
NCLV	*959*	*18.55*	*17.50–19.64*	*810*	*18.79*	*149*	*17.35*

ACAOS, anomalous origin of the right or left coronary artery from an ectopic coronary artery with intramural course; *CI*, confidence interval; *CMP*, cardiomyopathy; *CVC*, cardiovascular condition; *DCM*, dilated cardiomyopathy; *ECG*, electrocardiogram; *HCM*, hypertrophic cardiomyopathy; *HO*, high origin; *hr* high risk; *L-ACAOS-IM*, left ACAOS from the right sinus (RSV) with an intramural course; *NC,* non-coronary sinus; *NCLV*, non-compaction left ventricle; *R-ACAOS*, right ACAOS; *WPW*, Wolff-Parkinson-White. NCLV is currently not considered a high-risk cardiovascular condition but is reported here because of the potential need for a new discussion of the entity, still under study.(Source: Angelini [32]. Reproduced with permission of Springer Nature.)

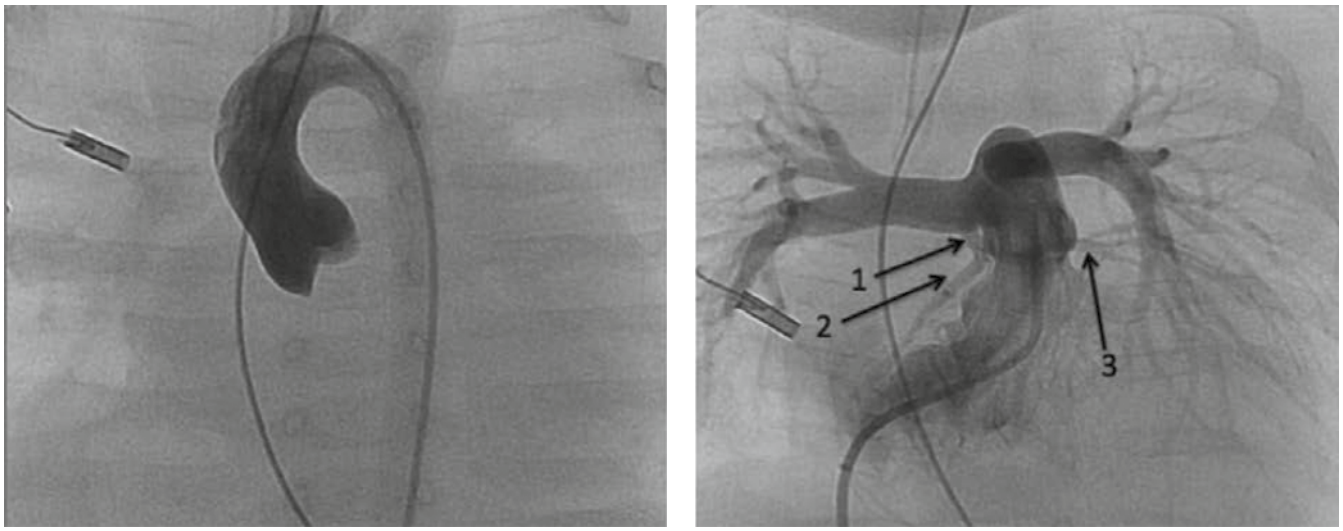
Anomalous pulmonary origins of the coronary arteries: incidence, anatomy, and natural history

These are rare lesions with the commonest and most important being anomalous left coronary artery arising from the pulmonary artery (ALCAPA) with an incidence of only 1 in 300,000 live births. ALCAPA presents early in life with a mortality of up to 90% in the first year, if untreated. Anomalous right coronary artery from the pulmonary artery (ARCAPA) is even rare, usually presenting after a few years of life, but with a wide clinical spectrum. Later presentations are not infrequent and some adults with this condition are at risk of sudden death [36–38]. Common presenting findings in the adolescent or adult population include EKG changes (ST changes and Q waves), cardiomegaly, a pansystolic murmur, and echocardiographic findings of mitral regurgitation [39]. Extensive intercoronary collaterals from the right side of the heart and/or retrograde flow from LCA- derived collaterals back to the pulmonary artery are also often seen in these older ALCAPA patients [30].

Anomalous right coronary artery from the pulmonary artery may be more benign than ALCAPA, as the right ventricle, which is supplied by the ARCAPA, has more favorable myocardial oxygen supply and demand characteristics when compared with the left ventricle. Other, even rarer variants include both right and left coronary arteries arising from the pulmonary artery, anomalous single coronary artery from the pulmonary artery (ASCAPA) (images with permission) as well as accessory coronary artery arising from the pulmonary artery [40] (Figure 31.13). The rest of this discussion will be restricted to ALCAPA.

Pathophysiology of ALCAPA

The pathophysiology of ALCAPA is complex and will vary with the exact anatomy and the changing physiological circumstances as the neonate develops and pulmonary vascular resistance (PVR) and pressure falls. The ALCAPA vessel provides a connection between the pulmonary artery and the myocardium supplied by the left coronary artery. Left ventricular coronary perfusion is dependent on diastolic perfusion, as the pressure generated by left ventricular contraction prevents coronary perfusion during systole. In the early neonatal period, PVR and pulmonary artery pressure are high, compared with later in life. In this phase, the left ventricle may have adequate oxygenation, albeit with mixed venous blood with relatively low hemoglobin oxygen saturation, which can be adequate for left ventricular function. As PVR and pulmonary artery pressure decrease, flow in the ALCAPA vessel may reverse, acting as a fistula and causing run-off of coronary blood flow to the pulmonary artery, creating a "coronary artery steal" and worsening left ventricular perfusion. This will cause ventricular ischemia, which will lead to ventricular dysfunction, especially in diastole, which will lead to an increase in left ventricular diastolic pressures, thus further decreasing the perfusion pressure. The "coronary steal" may also affect right ventricular perfusion in both systole and diastole, if there are significant collaterals, but the presence of some systolic perfusion of the right ventricle muscle, as in normal coronary physiology, is protective. A peculiar potential benefit of the reverse flow in the ALCAPA vessel (towards the pulmonary origin) is that this may help to maintain PVR and pressure, potentially delaying the onset of symptoms.



(A) (B)

Figure 31.13 Anomalous single coronary artery arising from the pulmonary artery. (A) Aortogram with absent coronary ostia. (B) Coronary filling after contrast injection into the pulmonary artery demonstrating a short single coronary artery (1) bifurcating into right (2) and left (3) branches. (Source: Machovec et al. [40]. Reproduced with permission of Wolters Kluwer Health, Inc.)

The worsening left ventricular function will be associated with dilation of the left ventricle. Left heart dilation may be associated with a shift of the interventricular septum towards the right, with associated impairment of right heart function. Mitral valve regurgitation can be induced by both dilatations of the left atrioventricular ring and ischemic dysfunction of the papillary muscles. This will lead to volume loading and further deterioration of left ventricular function with worsening pulmonary congestion and a low output state. The commonest presentation of ALCAPA is at weeks to sometimes months after birth with a condition that is essentially a severe dilated cardiomyopathy of ischemic origin. All infants presenting with dilated cardiomyopathy must be closely screened for anomalies of coronary origin.

Variations in the anatomy of the ALCAPA may influence the presentation. As with normal coronary arteries, there may be significant differences in the balance of these arteries. The more that the right coronary is dominant, supplying significant portions of the ventricular septum and other regions of the left ventricle, the more likely it is that there will be a later presentation with less severe deterioration in myocardial function. Similarly, stenosis of the ALCAPA vessel, which may occur at its origin, will actually lessen the impact of the coronary steal and allow more chance for collateral vessels from the right coronary to perfuse the left side of the heart. There is some evidence that these more delayed presentations may have a long-term negative impact, as the underlying ischemia will have been more long-lasting, producing fibrosis, and ventricular recovery after repair will be impaired. For patients with a dominant ALCAPA distribution, presentation is likely to be early with severe myocardial dysfunction. Although recovery in this circumstance can be excellent, some patients may have completed infarction of regions of the left ventricle with no prospect of recovery of function with reperfusion, and with a risk of formation of aneurysm of the left ventricle. The more severe early presentations are also at risk of lethal complications before surgical repair can be performed. Additionally, about 10–15% of ALCAPA patients are adult-type which without surgical repair results in a risk of sudden death before the age of 35 in 80–90% patients. It is for this reason that surgical repair of all those diagnosed as adolescents or adults is recommended [41].

Surgery for ALCAPA

Historically, simple ligation of the ALCAPA vessel was used, improving survival [42]. This would prevent the coronary steal and, depending on the adequacy of collateral circulation, improve perfusion of the left ventricle. Mortality was still high and recovery of left ventricular function usually incomplete. This procedure is no longer performed in major congenital cardiac surgery centers. Current surgical management involves restoring aortic perfusion of the ALCAPA vessel, thus providing a two-coronary circulation originating from the aorta, usually by mobilization and reimplantation of the ALCAPA vessel onto the aorta [43–45] (Figure 31.14). A specific example that can be used for a very short ALCAPA vessel is the Takeuchi procedure. This involves using an intra-arterial pulmonary baffle to direct flow from a surgically created aortopulmonary window to supply the origin of the ALCAPA vessel with systemic arterial blood in situ, with patch expansion of the pulmonary artery to allow space for the baffle and prevent pulmonary obstruction [46–48] (Figure 31.15).

The unit managing these cases should be able to provide extracorporeal circulatory support with a ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO) if required. The techniques may be necessary as part of preoperative resuscitation or for support of the patient in the early postoperative period, as the recovery of myocardial function is usually not immediate [49]. Imamura et al. reported a series of 26 ALCAPA operations over a 20-year

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period [50]. Twenty-one patients did not require ECMO support and five required ECMO for a mean of 10.7 ± 6.7 days. One patient in each group required cardiac transplantation, and four others required six reoperations (five for MR). There were no deaths in the series, and actuarial freedom from transplantation or reoperation at 5 years was 0% in the ECMO group, and 92% in the non-ECMO group. Chapter 37 presents a detailed discussion of mechanical support of the circulation.

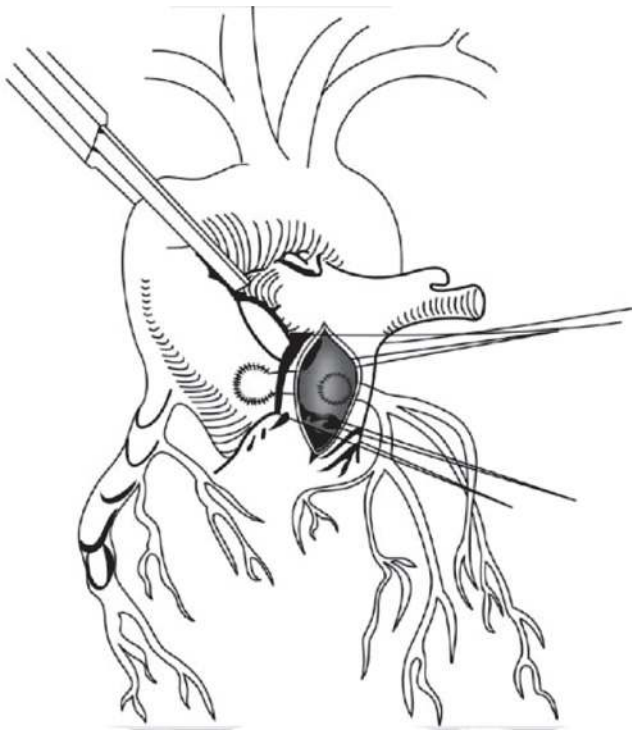


Figure 31.14 Direct aortic reimplantation of the anomalous left coronary artery from the pulmonary artery. The anomalous ostium is excised with a button of the pulmonary artery wall. This button is then implanted into the left lateral side of the ascending aorta. The resulting defect is closed with a pericardial patch (Source: Arciniegas [45]. Reproduced with permission of Elsevier.)

There is controversy about the role of surgical procedures to improve mitral valve regurgitation at the primary operation because mitral valve function usually improves as improved myocardial function results in decreased end-diastolic volume and better papillary muscle function [51]. In a series of 25 operations for ALCAPA, Kudumula et al. repaired the mitral valve only for moderate to severe MR, accompanied by structural mitral valve abnormalities, observed in four patients [52]. Two patients had mitral valve cleft, one had a prolapse, and one had a dysplastic double orifice mitral valve. One patient with a structural mitral valve abnormality that was not repaired at the original operation developed severe MR and required repair at a second operation. Of 14 patients in the series without structural mitral valve problems with moderate or severe MR, 13/14 had none or mild MR at the time of follow-up. A Saudi Arabian retrospective observational cohort of 29 patients from 1999 to 2018 analyzed by Ismail showed similar findings (Figure 31.16). Spontaneous regression of MR was reported by Ismail et al. In these patients, LV systolic function showed echocardiographic improvement within 6 weeks and returned to normal within 1 year's time and in addition somatic growth of children improved 6 months after surgical repair [53]. Some surgeons still argue that there is a reasonable argument that surgical techniques that decrease the mitral valve annulus size but allow for future growth may improve mitral valve function acutely, improving the performance of the dysfunctional early postoperative heart. Although repairing the mitral valve does increase the cross-clamp time on an already ischemic myocardium, this does not seem to have a clinically significant effect on the later normalization of LV function or other postoperative outcomes. According to a 2016 study by Naimo et al. which evaluated 42 ALCAPA patients, late reoperation was uncommon in the 33 patients who did not undergo concomitant MV repair despite MR ranging from none to severe. In fact, late MV reoperation was only needed in 14% at 5 & 10 years, and 19% in 20 years after original surgery. Persistent MR does

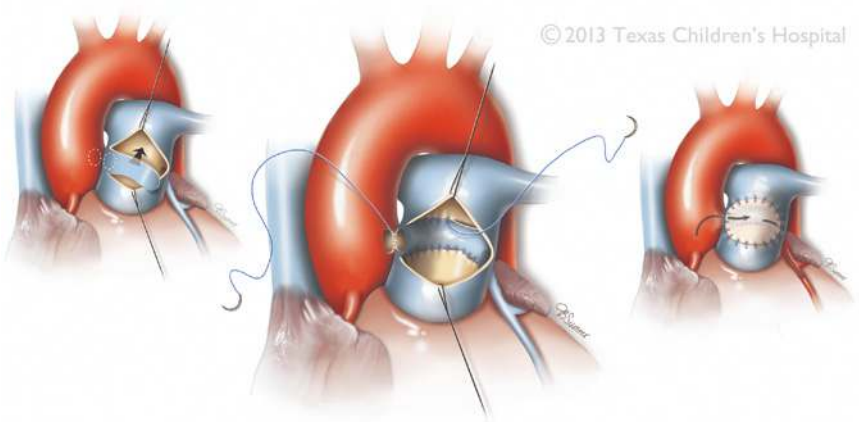


Figure 31.15 Takeuchi procedure through median sternotomy with extracorporeal circulation and cross-clamped aorta. Left: The tunnel for coronary flow has been made between the aorta and the anomalous left coronary artery by means of a flap of pulmonary artery wall. Middle: Construction of the tunnel to direct flow from the aortic root to the anomalous left coronary artery. Right: The pulmonary artery is then reconstructed with pericardium. (Source: Reproduced with permission of Texas Children's Hospital.)

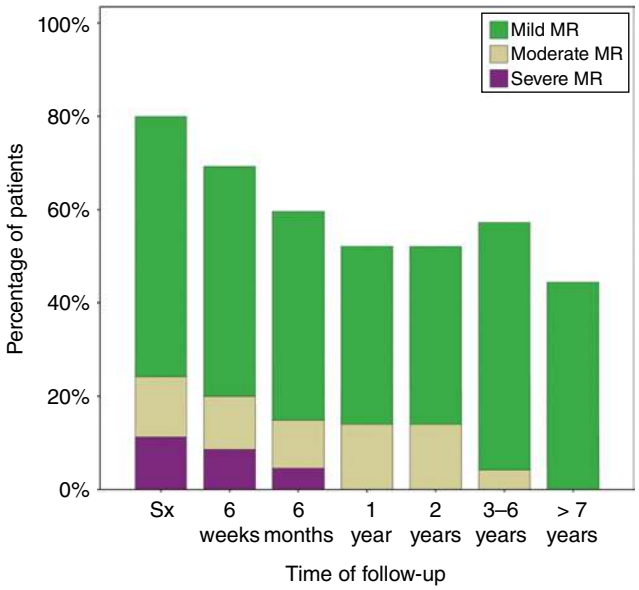


Figure 31.16 Spontaneous regression of mitral regurgitation after ALCAPA repair. MR, mitral regurgitation. (Source: Ismail et al. [53] / Cureus / CC BY 4.0.)

warrant close followup and late MV operative repair may eventually be necessary in some patients [54].

Anesthetic considerations for ALCAPA

The degree of myocardial dysfunction is the factor that dominates the condition and prognosis of these patients throughout the perioperative period. Preoperatively, the patient with ALCAPA may be receiving cardiorespiratory support, ranging from none to an intubated ventilated patient on ECMO. In between these extremes will be patients with various degrees of inotropic support receiving tailored vasodilators or, in some cases, vasoconstrictors. The general principle that a failing heart, especially with MR, will have output improved by systemic vasodilation is sound, but the severity of the dysfunction in some of these patients means there may be a role for vasoconstrictors. If the patient is already hypotensive, it is possible that the vasodilation is actually excessive for that heart and results in greater tachycardia. The poor coronary perfusion is worsened by both systemic hypotension and tachycardia. In this scenario of myocardial dysfunction with relatively excessive vasodilation, judicious use of vasoconstrictors may improve blood pressure and decrease heart rate, improving coronary perfusion while maintaining an acceptable cardiac output. The patient should be monitored for signs of the inability of the heart to cope with the increased afterload or worsening MR.

Preoperative assessment of patients with ALCAPA should also include assessment of the complications of the myocardial dysfunction, such as respiratory, renal and hepatic dysfunction, as well as a general medical review.

The group of patients with ALCAPA who provide perhaps the greatest challenge for the anesthesiologist comprises those who have been diagnosed after presenting with respiratory distress, but who are stable and do not require acute cardiorespiratory support. They may have intravenous access, and non-invasive monitors have been used for them. Echocardiography will have confirmed the diagnosis and the critically poor myocardial function. The anesthesiologist will be responsible for the induction of anesthesia and stabilization of the patient prior to the initiation of CPB in a situation where minor changes in sympathetic drive or myocardial function might be associated with cardiac arrest. Induction of anesthesia, intubation, positive pressure ventilation, placing a central venous catheter or transesophageal echocardiography (TEE) probe, excessive anesthesia with myocardial depression or depression of central nervous system-driven sympathetic activity, or inadequate anesthesia resulting in excessive sympathetic response can all lead to life-threatening incidents. The anesthesiologist should be prepared to heparinize and defibrillate the patient at any time. The nursing, perfusion, and surgical team should all be prepared for the potential need for emergent sternotomy and initiation of CPB, and they should be in the operating room during the induction of anesthesia. If it is possible to obtain preinduction arterial access without upsetting the patient, this is highly desirable for the earliest warning of cardiovascular compromise. This can sometimes be accomplished in young infants with local anesthesia, either topically or by injection, along with 50% N_2O inhalation or small analgesic doses of fentanyl or other opioids intravenously.

The induction of anesthesia in patients with ALCAPA requires great care in the slow titration of small increments of whatever drugs are selected to minimize the myocardial depression and vasodilation that accompanies the usual doses of most of these drugs. Opioids, such as fentanyl and remifentanil, although tending to spare myocardial function, can rapidly depress central sympathetic drive, causing relative bradycardia and vasodilation, which may be poorly tolerated by these patients. Similar problems can arise even with drugs, such as etomidate and ketamine, that tend to preserve sympathetic function and cardiovascular stability in normal patients. Ketamine is a direct myocardial depressant, and these hemodynamic effects are most commonly seen in the patient who has depletion of endogenous catecholamines, such as the infant with ALCAPA. Ketamine is also implicated as possibly inducing brain injury in the developing brain and some anesthesiologists avoid it in this age group. The complex risk balance of choice of agent and combination of agents for ALCAPA patients makes judicious, cautious use of agents with which the anesthetist is very familiar a reasonable choice.

Preoperative fluid restriction to manage pulmonary congestion may make the patient especially prone to hypotension with the initiation of positive pressure ventilation. Judicious intravascular volume loading at this time may prevent this. Successful transition to anesthesia and positive pressure ventilation may improve lung function and create some afterload reduction, which may improve left ventricular function. Lung compliance is usually low due to pulmonary congestion, and significant ventilator pressures are commonly required.

Maintenance of elevated PVR will minimize the "coronary steal" due to the ALCAPA flow into the pulmonary artery. Avoiding a high inspired oxygen concentration and maintaining a normal or moderately high arterial carbon dioxide

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level are key strategies for maintaining PVR, but pulmonary congestion secondary to left heart failure may mean that increased inspired oxygen levels and high ventilator pressures will be required. Significant PEEP may serve both to improve function in the congested lung and to maintain PVR. Increasing ventilatory pressures, particularly PEEP, will require attention to maintaining adequate intravascular volume to support ventricular filling and avoid low cardiac output and systemic hypotension.

Rapid repetitions of non-invasive blood pressure monitoring should be continued until intra-arterial continuous blood pressure monitoring is available. Adequate monitoring of the circulation, respiration, and depth of anesthesia in these patients requires constant vigilance. It is advantageous to have at least one, and perhaps two, other pairs of experienced hands to perform the procedures required to prepare the patient for surgery after induction of anesthesia, so one anesthesiologist can focus on the monitoring and anesthesia.

Patients with ALCAPA who have been intubated, ventilated and had appropriate vascular access obtained preoperatively may be sicker in many respects than the previous scenario, but the anesthesiologist will have to make less of a transition for the patient to anesthesia and establish invasive monitoring and other preparation. It is still important that there is great vigilance in the transfer of the patient to the operating room and that the whole operative team is present to initiate CPB at short notice before the transfer commences. Patients who have already been placed on mechanical circulatory support present challenges in transfer, but provided, there is no interruption to that support, they are very safely supported. The anesthesiologist must ensure the patient has adequate intravascular volume to allow good venous drainage into the external mechanical circuit. Monitoring the inlet pressure of the circuit can greatly assist this process.

Delivery of cardioplegia in patients with ALCAPA requires variation from routine procedures. Ensuring adequate cardioplegia flow to all the myocardium is crucial for the preservation of myocardial function. Usually, this can be achieved by anterograde delivery of cardioplegia via both the normally placed right coronary and the anomalous left coronary, the latter usually achieved by cannulating and perfusing into the pulmonary artery clamped so that that flow is restricted to the ALCAPA vessel.

After the cross-clamp is removed and the heart is perfused, recovery of electrical and motor function of the heart may be slow. As long as the heart is not distending, perfusion pressure and myocardial perfusion are adequate, allowing the heart considerable time to eject without the work of supporting the full circulation, which is beneficial for myocardial recovery. Forcing the heart to support the circulation with early weaning from CPB and administration of large doses of inotropes carries a high risk of return to CPB and of causing myocardial injury. TEE is crucially important in these infants to assess myocardial function and the degree of MR after repair.

Translocation of a coronary artery has the major risks of bleeding from the suture line and poor flow in the coronary, leading to myocardial ischemia and poor function. Blood loss may be minimized by reversal of heparin (as far as possible, but may be limited by the need for mechanical support of the circulation), by optimizing coagulation with appropriate blood products and the use of an antifibrinolytic. Concern about thrombotic and embolic complications may deter some pediatric cardiac units from using these agents. Poor function of the translocated ALCAPA vessel may require revision of the surgery.

These patients are at significant risk for myocardial failure and circulatory collapse after weaning from CPB. Depending on the circumstances, leaving the sternum open and closing the skin with a membrane and dressing may be safer than formal closure of the chest. Not closing the sternum will prevent early pressure on the heart and allow room for some postoperative swelling without compression of the heart. The membrane closure also allows rapid access for resuscitation and return to bypass in the early postoperative period. Purse strings for cannulation for bypass may be left in place during this period and removed when the chest is formally closed. For patients who are less stable in the operating room, transitioning from a CPB circuit with venous reservoir to other mechanical support such as left ventricular assist device, biventricular assist device or ECMO will provide circulatory support of the patient while the myocardium recovers and improves function. Occasionally, failure to wean from CPB for other operations, i.e., ventricular septal defect (VSD) with left ventricular dilation and failure, may be due to an unrecognized ALCAPA; Callagan et al. reported this occurrence in a 6-week-old patient where pulmonary hypertension was suspected to have prevented severe left ventricular dysfunction, decreased the symptoms and masked the diagnosis of ALCAPA [55]. Coronary angiography confirmed the ALCAPA diagnosis, and emergency reoperation, repair of ALCAPA, and postoperative ECMO were necessary to ensure successful outcome.

KEY POINTS: ALCAPA

- ALCAPA presents with ischemic cardiomyopathy in the first few months of life.
- Decrease in PVR may create a coronary steal phenomenon.
- Early operation within days of diagnosis is recommended, due to the risk of sudden death.
- The risk of circulatory collapse at induction of anesthesia and in the pre-bypass period is high. Immediate institution of CPB should be available.
- Induction of anesthesia should be titrated with monitoring and cardiovascular support.
- Maintenance of both pulmonary and systemic vascular resistance (SVR) is important.
- Translocation of the ALCAPA to the aorta is the operation of choice.
- Availability and a reasonably low threshold for mechanical support (VAD/ECMO) are important considerations.
  - Long-term outcomes after ALCAPA repair are very good
  - Although early operation on the mitral valve remains controversial, early repair is often performed when mitral regurgitation is severe

Anomalous aortic origins of the coronary arteries

Some of the abnormalities historically thought to be benign have more sinister subgroups where coronary perfusion may be jeopardized in certain circumstances and sudden death may occur. Abnormal origins of the coronary arteries from the aorta are most commonly benign; however, if these abnormalities involve a left coronary artery arising from the right coronary sinus (0.15% in adult cardiac catheterization series) and the course of the vessel passes between the aorta and pulmonary artery, then there is a risk of myocardial ischemia with angina and sudden death, especially with exercise. A right coronary artery arising from the left coronary sinus (0.92%) with the vessel passing between the aorta and pulmonary arteries is also associated with sudden death. Most of the variants of the abnormal location of the origin of the coronary artery from the "opposite" coronary sinus do not have the vessel taking a course between the aorta and pulmonary artery and do not appear to be at higher risk. Where the coronary artery does pass between the aorta and pulmonary arteries, it is postulated not only that exercise increases the risk of myocardial ischemia due to increased oxygen demand in the face of some obstruction to flow as a result of constriction between the aorta and pulmonary artery, but also that the increased cardiac output associated with exercise may cause distension of the root of these vessels, especially the elastic pulmonary artery, and worsen the obstruction of the coronary vessel "sandwiched" between the two great arteries.

Deciding about therapy is difficult in the scenario where the first symptom may be sudden death but the lesion may also be benign. Criteria for intervention are based on evidence of obstruction, symptoms, exercise testing, and detailed imaging to quantify lateral compression, and hypoplasia or stenosis associated with the anomaly, especially as there is commonly an intramural portion that may be narrow. Therapeutic approaches have included beta-blockers and/or advice to avoid exercise with substantial effort; cardiological intervention with stenting; and surgery, which may involve rerouting the vessel, unroofing a narrow intramural portion, or providing an alternative inflow by graft or aortic side-to-side anastomosis, distal to the narrow compressed segment [56, 57].

Congenital atresia of the left main coronary artery

Congenital atresia of the left main coronary artery (CALM) is a rare, apparently benign anomaly. It is distinguished from "single coronary artery," where the single vessel has two main branches with distributions similar to the normal left and right coronary arteries, in that CALM has the distribution to the left heart filled retrograde by collaterals. There is an association with supravalvular aortic stenosis, especially Williams syndrome, with coronary anomalies, including CALM, which are associated with intermittent ischemia and sudden death (see later).

Coronary arteriovenous fistulas: incidence, anatomy, and natural history

Coronary arteriovenous fistulas (CAVFs) occur in only 1 of 50,000 live births but are noted in 1 of 500 patients having cardiac catheterization. In those with a congenital fistula, associated CHD occurs in 20–45%. Congenital fistulas may represent the persistence of embryonic sinusoids that provide myocardial blood supply by cross-connecting the lumen of the primitive tubular heart. Although called "arteriovenous," the distal connection is usually to the right side of the circulation but not necessarily to a vein, and termination in any chamber of the heart or in the pulmonary artery is possible [58] (Figure 31.17). CAVF can also be acquired as a

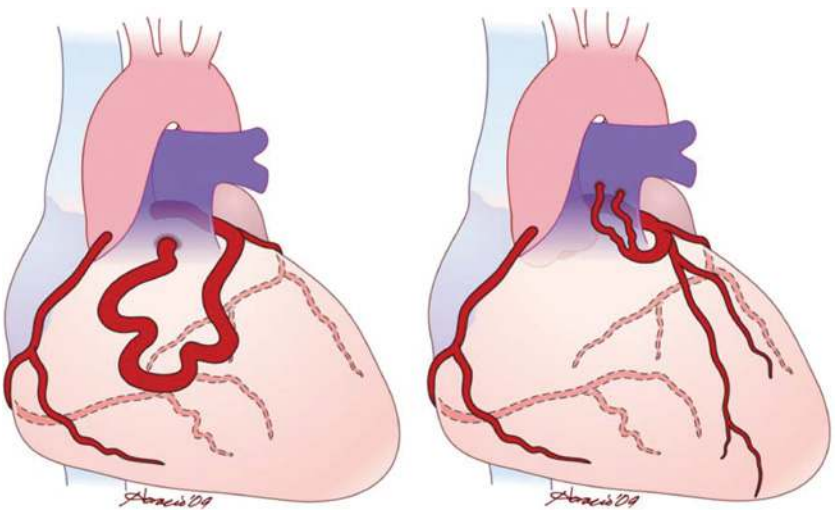


Figure 31.17 Two types of coronary-to-pulmonary artery fistulae (CPAF). (A) There is a single prominent fistulous connection between the left main/left anterior descending artery and the main pulmonary trunk. (B). There are multiple small-caliber fistulous connections between the left main/left anterior descending artery and the main pulmonary trunk. Although both types of CPAF involve the same vessels, anecdotally the CPAF patients with morphology resembling (A) were more likely to be symptomatic as there was greater hemodynamic effect when compared with CPAF patients with morphology resembling (B). (Source: Verdini et al. [58]. Reproduced with permission of Wolters Kluwer Health, Inc.)

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result of abnormal connections made by, for example, trauma, including surgery or cardiological intervention, infection, or ischemia. CT angiography with MDCT (multiple detector computed tomography) is now the test of choice for diagnosing CAVF. It has a short examination time and superior spatial and temporal resolution [58].

CAVFs may be subclassified by angiographic appearance as *type A*, where the coronary artery is dilated proximal to the fistula, but continues with the normal coronary vessel arborizing in the myocardium distal to the fistula; and *type B*, where the coronary artery is dilated over the entire length and terminates on the right side of the heart. These categories may determine management, as suitability for catheter occlusion and surgical approach will depend on the anatomy.

CAVFs may present as incidentally detected asymptomatic murmurs. The natural history is very variable and largely depends on the size of the shunt created, the development of complications (see the next section) and associated conditions. Some smaller fistulas have been noted to close spontaneously [59]. There are currently no established guidelines for deciding whether, or how to treat coronary fistulas [58].

Pathophysiology of CAVFs

Although often incidental findings, there are a number of mechanisms by which these anomalies can produce serious complications. As a connection between a high-pressure and a low-pressure part of the circulation, a high-speed turbulent jet may be created which may be the substrate for subacute bacterial endocarditis or for development of abnormalities of the supplying vessel, with fibrosis, stenosis, and aneurysm formation possible, and with consequent thrombosis, embolus, or rupture of a coronary vessel causing myocardial ischemia or sudden death. Myocardial ischemia may also arise from a coronary steal, with perfusion pressure in related coronary vessels becoming critically low due to the run-off down the sinus. If there is a high flow through the fistula, this may be sufficient to create significant volume loading with heart failure or pulmonary hypertension.

Surgery and catheter treatment of CAVF

There is controversy about whether asymptomatic fistulas should be treated, but some suggest that prevention of complications warrants intervention for all CAVFs. Others are more conservative, noting that spontaneous closure of some small fistulas has been observed and all interventions carry non-trivial risk and favor monitoring and conservative management. Some fistulas are suitable for catheter occlusion techniques if they are accessible and there is a low risk of coil embolus or interruption of distal coronary perfusion.

Surgical interruption of the fistula is the most common treatment. Some may be suitable for proximal ligation on the epicardial surface with a beating heart without CPB. Care must be taken to ensure that there is no myocardium that will become ischemic with ligation of the fistula. To preserve branches that provide myocardial perfusion, some fistulas will require ligation at their termination, which will usually require CPB.

Anesthesia for CAVFs

Anesthesia will be determined by the procedure planned and the complications that the patient has developed. If CPB and an open procedure are planned, the potential for the fistula to jeopardize myocardial protection must be carefully considered and managed. Run-off of the cardioplegia solution down the fistula may result in failure of myocardial protection for substantial segments of the myocardium. Controlling the fistula and then providing more cardioplegia may be warranted. Catastrophic failure of myocardial preservation has been seen to occur in cases where a fistula was undiagnosed or uncontrolled and where other associated congenital lesions were being repaired. Bacterial endocarditis prophylaxis is recommended for all patients with coronary artery fistulas [58].

Coronary artery bridging, aneurysms, and stenosis

Coronary artery bridging represents a common normal variant, with the coronary artery having a segment of the intramural course. Occasionally, this may be associated with stenosis or dynamic occlusion, which may require intervention. It is rare for this diagnosis to be the primary indication for surgery in pediatric practice. In pediatrics, coronary bridging most commonly presents as technical problems for the surgeon, which may complicate surgery and be associated with coronary injury, sometimes producing ischemia and poor function after the surgical procedure.

Coronary aneurysms may be congenital, but acquired lesions due to Kawasaki disease are more commonly encountered in pediatric practice. It is rare that there are surgical or catheter interventions for these lesions, but anesthesia for imaging procedures may be required.

Congenital stenosis of the coronary arteries is rare. Lesions of the left coronary artery may be associated with sudden death. Acquired stenosis may occur in childhood as a result of precocious atheromatous disease in familial hyperlipidemia, secondary to the abnormalities of the aortic root due to arteritis or connective tissue disorders, or in relation to fibrosis arising from turbulence due to regional anatomical abnormalities.

Coronary artery abnormalities associated with supravalvular aortic stenosis

Surpravalvular aortic stenosis, commonly associated with Williams syndrome, can result in abnormal coronary flow and sudden death. There are a number of case reports and series of these patients having circulatory collapse in association with anesthesia [60]. The most disturbing feature of these reports has been the absence of obvious precipitating factors, such as changes in heart rate or blood pressure. This has made anesthesiologists wary of these patients because resuscitation has been unsuccessful in a number of these cases once a cardiac arrest has occurred. These events are not well related to the degree of aortic obstruction, so the anesthesiologist may be falsely reassured that the risk is low, as with aortic valve obstruction of a similar degree.

The mechanisms for abnormal coronary flow in these patients are multiple. [61] There may be associated

congenital abnormality of the orifice of the coronary arteries. There may be a proximal congenital stenotic segment of one of the coronary arteries, the left being the most dangerous. Turbulence related to the abnormal anatomy combined with systolic hypertension proximal to the supravalvular stenosis may lead to acquired changes in the coronary orifice with obstruction secondary to fibrosis or atheroma. Diastolic hypotension proximal to the supravalvular stenosis may decrease diastolic perfusion on which the left ventricle is dependent. Interaction between the tip of the aortic valves and the stenosed aortic segment may result in obstruction to coronary perfusion, either chronically or potentially acutely in relation to a fleeting change in valve disposition.

In summary, patients with supravalvular aortic stenosis are at high risk of acute coronary events that may be triggered by subtle changes in the circulation. Resuscitation may not be possible should cardiac arrest occur. A detailed cardiological evaluation may inform the level of risk, but avoiding anesthesia prior to surgical repair of the lesion may be warranted. The surgical plan should deal with both the supravalvular obstruction and the mechanisms of coronary obstruction. The anesthesia induction should be considered high risk, with immediate availability of emergency access to CPB. Further details about supravalvular aortic stenosis, and its anesthetic and surgical management, are presented in Chapter 27.

Pericardial effusion and tamponade

Incidence, anatomy, and natural history

The pericardium is a double-layered sac in which the heart and base of the great vessels are invaginated. There is normally a minimal amount of fluid, about 10–50 mL, between the inner visceral and tough outer parietal layers. There is enough compliance in this sac to accommodate small amounts of fluid collecting with minimal pressure change. In the acute situation, further fluid collection will be in the face of very low compliance and generate a rapid increase in pressure, which will compress the heart, preventing ventricular filling and decreasing stroke volume. In the more chronic situation, slow accumulation of fluid may allow time for expansion of the pericardial sac and larger volumes to be accommodated with less myocardial compression (than smaller volumes accumulating acutely). Some useful parameters for characterizing pericardial effusions in adult-sized patients are listed in Table 31.5 [62].

A broad spectrum of pericardial syndromes can present with degrees of significance ranging from completely asymptomatic to life-threatening. Chronic inflammatory conditions may induce fibrosis of the pericardium with decreased compliance of the pericardium and potential for a thick pericardium to tightly encase the heart, creating chronic constrictive pericarditis [63, 64]. Chronic pericarditis may be caused by tuberculosis. There are many causes of pericardial disease. In 2015 the European Society of Cardiology (ESC) proposed an updated classification system for pericardial diseases which has been endorsed by the American Society of Cardiology (ACC) [65] (Table 31.6). Tuberculosis is considered the most important world-wide cause of pericardial disease. It widely affects developing countries where this bacterial infection is endemic and is often seen associated with HIV infection [65]. Pericardial disease often requires a combination of procedural and medical management. The acute medical management of pericarditis has historically involved anti-inflammatory medications such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Two significant clinical trials by Imazio et al. in 2010 and 2014, known as the COPPS (Colchicine for the Prevention of the Post-Pericardiotomy Syndrome) and COPPS 2 (Colchicine for the Prevention of the Post-Pericardiotomy Syndrome and Postoperative Atrial Fibrillation), respectively, showed a statistically significant reduction in PPS (Post-Pericardiotomy Syndrome) using colchicine, an anti-inflammatory derived from the autumn crocus plant often used for the treatment of gout. Since these favorable randomized trials colchicine is now a Class 1A agent not only for prevention but also for *treatment* of acute

Table 31.5 Classification scheme for pericardial effusions in adult-sized patients

Onset:
Acute versus chronic
Size:
Small
50–100 mL (or TTE-derived **single** dimension at end-diastole <10 mm)
Medium
100–500 mL (or 10–20 mm on TTE)
Large
>500 mL (or >20 mm on TTE)
Extent:
Localized versus **circumferential**
Hemodynamic impact:
Insignificant versus significant (i.e., cardiac tamponade)
Fluid composition:
Transudate versus exudate

Abbreviation: TTE, transthoracic echocardiography.
Source: Tuck & Townsley [62]. Reproduced with permission of Elsevier.)

Table 31.6 Classification of pericardial diseases

Infectious causes
Viral (presumed to be the most important cause in developing countries)
Bacterial (especially tuberculosis)
Fungal (very rare)
Parasitic (very rare)
Non-infectious
Autoimmune (common): systemic inflammatory diseases, auto-inflammatory diseases (e.g., Familial Mediterranean Fever)
Neoplastic (common as secondary metastatic involvement: lung, breast cancers, lymphomas)
Metabolic
Traumatic and iatrogenic (common, especially as post-cardiac injury syndrome, e.g., post-pericardiotomy syndrome)
Drug-related (rare)
Other (uncommon)

Source: Imazio et al. [65]. Reproduced with permission of Wolters Kluwer Health, Inc.

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and recurrent pericarditis and post-cardiac injury syndromes [62]. Pericardial disease can have significant long-term consequences. Pericardial effusions should be considered a marker of the severity of underlying disease and when idiopathic are often the first incidental finding of unrecognized disease [66]. A meta-analysis of over 10,000 patients in 2011 by Mitiku et al. showed that the presence of even a small and asymptomatic pericardial effusion (of any cause) increases all-cause mortality; thus, early recognition and therapy are extremely important [67].

Pericardial effusions can be broadly divided into inflammatory and non-inflammatory causes [68] (Table 31.7). Within the pediatric congenital cardiac population conditions associated with tissue edema and capillary leak, such as heart failure or the high venous pressures of a poorly functioning Fontan circulation can be causes [69]. The most common cause of pericardial effusion and tamponade in this subgroup are due to complications after surgical interventions. Cardiological interventions, such as the use of wires, balloon catheters and taking biopsies, and occasionally some anesthesia procedures, such as central venous cannulation, can all result in perforation of the heart and hemorrhage into the pericardium [70, 71]. A detailed history and physical examination with considering the clinical context often point to the cause of an effusion. Any pericardial disease may cause tamponade, but the pre-existing condition and background of the patient may help decide the probability for borderline cases. A Working Group on Myocardial and Pericardial Diseases for the European Society of Cardiology studied the epidemiology of pericardial disease that progresses to tamponade and formulated a triage strategy outlining which conditions are least or most likely to progress to tamponade [72] (Table 31.8).

There are multiple mechanisms for pericardial collections to form as a result of cardiac surgery. Postpericardiotomy syndrome (PPS) may occur after 15–30% of open-heart procedures in children. The incidence is much lower, <2%, after closed procedures. The mechanism is immune-mediated with anti-heart antibodies almost always present. Previous suggestions that these reactions are commonly also linked to new or reactivated viral infections have been questioned in more recent studies. Although there is unpleasant and prolonged hospital stay, PPS only rarely leads to tamponade or death. Steroid prophylaxis does not prevent this condition in children and may lead to a worse course with an increased percentage needing drainage. Steroid treatment of PPS makes a modest impact on the recovery profile [73]. PPS is usually managed with NSAIDS and/ or colchicine and may

Table 31.7 Causes of pericardial effusions

Inflammatory
Infectious:
Viral: enteroviruses (coxsackie B, echoviruses), adenovirus, herpesviruses (EBV, CMV, VZV), parvovirus B19, HIV, HCV
Bacterial: Mycobacterium (tuberculosis, avium-intracellulare), gram positive cocci (Streptococcus, Staphylococcus), Mycoplasma, Neisseria (meningitides, gonorrhea), Coxiella burnetii
Fungal: Histoplasma species, Candida species
Protozoal: Echinococcus species, Toxoplasma species
Cardiac injury syndromes: post-pericardiotomy, post-myocardial infarction, post-electrophysiology or coronary interventions
Autoimmune: systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), familial Mediterranean fever
Uremic pericarditis
Drug hypersensitivity
Non-Inflammatory
Neoplastic: primary tumors (mesothelioma, sarcoma), secondary (lung and breast cancer, lymphoma)
Metabolic: hypothyroidism (myxedema coma), severe protein deficiency
Traumatic: iatrogenic, direct/indirect pericardial injury (penetrating or blunt chest wall injury, and aortic dissection Reduced lymphatic drainage: congestive heart failure, cirrhosis, nephrotic syndrome

Abbreviations: CMV = cytomegalovirus; EBV = Epstein Barr Virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.
Source: Vakamudi et al. [68]. Reproduced with permission of Elsevier.

Table 31.8 Causes of pericardial disease and precipitating factors causing cardiac tamponade

Likely to progress to cardiac tamponade
Neoplastic diseases
Infections (i.e., viral: EBV, CMV enteroviruses, HIV, bacterial, especially tuberculosis)
Iatrogenic hemopericardium
Post-traumatic pericardial effusion
Post-cardiotomy syndrome
Hemopericardium in aortic dissection and rupture of the heart after acute myocardial infarction
Renal failure
Rarely progressing to cardiac tamponade
Systemic autoimmune disease
Autoreactive pericardial effusions
Hypo- or hyperthyreosis
Early and late pericarditis (Dressler's syndrome) in acute myocardial infarction
Any other etiology of pericardial disease (i.e., cholesterol pericarditis, chylopericardium)
Never progressing to cardiac tamponade
Pericardial transudates caused by heart failure or pulmonary hypertension
Pericardial transudates in the last trimester of normal pregnancy
Precipitating factors
Drugs
Antihypertensive medications
Anticoagulants, thrombolytics, etc.
Injury
Complex PCI
Pacemaker implantation
Endomyocardial biopsy
Recent cardiac surgery
Indwelling instrumentation
Blunt chest trauma
Septicaemia
Dehydration, diuretics (reduced circulating volume)

Source: Ristić et al. [72]. Reproduced with permission of Oxford University Press.

occasionally need drainage of the effusion. Hemopericardium may arise from a specific source (or sources) of surgical bleeding, but it is more common for the postoperative bleeding to arise from raw surfaces, and conservative treatment, dealing with any clotting abnormality and having adequate surgical drains in place, will usually prevent the development of tamponade and the need for reoperation. If the bleeding persists or tamponade develops, surgical exploration will be required. Bleeding in relation to the removal of surgically placed intracardiac vascular catheters and temporary pacing wires may occasionally be rapid and lead to cardiac tamponade. Protocols for close monitoring after a line or lead removal, with elective echocardiography to look for an effusion some hours later (or earlier if there is a clinical suspicion of bleeding), have allowed earlier diagnosis of complications. Prolonged duration of effusion can occur in relation to lymphatic interruption, with the effusion being chylous if feeding has resumed. Patients who do not tolerate conversion to a completed Fontan circulation may also develop long-term effusions

Pathophysiology and diagnosis of cardiac tamponade

Tamponade is a life-threatening compression of the heart, which can occur slowly or rapidly, due to the pericardial accumulation of fluid, pus, blood, clots, or gas as a result of inflammation, trauma, aortic dissection, or cardiac rupture [74]. Eventually, the pericardial compliance will reach a limit beyond which even a small increase in fluid volume will lead to a rise in pressure that will cause tamponade physiology [75] (Figure 31.18). The pathophysiology of acute pericardial tamponade involves myocardial compression with restriction of ventricular filling. Venous pressure is raised. As stroke volume decreases, sympathetic stimulation will produce tachycardia to maintain cardiac output and systemic vasoconstriction to maintain systemic blood pressure. Venous and end-diastolic ventricular pressure will rise as the tamponade progresses, and tachycardia and systemic hypotension will become more severe. The minimum pressure in any chamber or great vessel compressed by the tamponade will be the pressure generated by the tamponade, so eventually all intracardiac pressures will equalize [76]. The *normal* inspiratory drop in pulmonary vascular resistance results in increased venous return to the right ventricle (RV) and only a small drop in the left ventricular (LV) filling pressure gradient, resulting in a physiologic drop in systolic blood pressure of <5 mmHg. As fluid collects in the pericardium during tamponade this drop is *accentuated* and during inspiration in the tamponade condition LV diastolic filling pressure remains high (from high pericardial pressure) which causes a decline in the filling pressure gradient thus causing an *even more exaggerated* drop in stroke volume [68]. Figure 31.19 explains these respiratory influences on cardiac filling.

Further compromise to myocardial function during tamponade can arise due to myocardial ischemia, even in patients with normal coronary arteries. Severe tamponade will cause systemic hypotension and high end-diastolic ventricular pressure, which will produce a low coronary perfusion pressure. Tachycardia will be associated with a very brief diastolic duration, the only phase of the cardiac cycle where the myocardium of the left ventricle is perfused. This combination of low perfusion pressure and inadequate time for perfusion can create myocardial ischemia. This will decrease myocardial function, with both diastolic and systolic dysfunction exacerbating the systemic hypotension and increasing end-diastolic ventricular pressure, creating a vicious cycle of worsening myocardial perfusion.

Cardiac tamponade can occur with an open pericardium. The space where the fluid is confined and pressure is created, which compresses the heart, depends on the procedure that has been done. Most cardiac procedures done through a sternotomy will involve opening the pericardium, and many repairs of CHD require harvesting of autologous pericardium for use as surgical patches. Usually, the pericardium is not closed with watertight suturing and it may be left wide open. In this circumstance, fluid collecting in the pericardium can emerge to occupy a larger space in the mediastinum. If drainage is inadequate, the physiological consequences of cardiac tamponade will still develop once the space fills to the point of relative

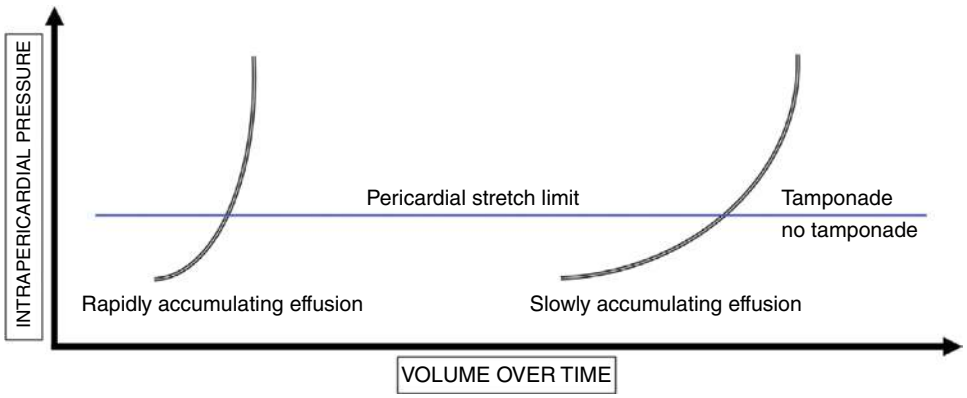


Figure 31.18 Tamponade physiology is predicted by the rate of rise of the effusion and the pericardial compliance. At a certain threshold, the pericardium's compliance will reach a pericardial stretch limit, where even a small increase in pericardial fluid volume will lead to the rise in intrapericardial pressure that causes tamponade. (Source: Alerhand & Carter [75]. Reproduced with permission of Elsevier.)

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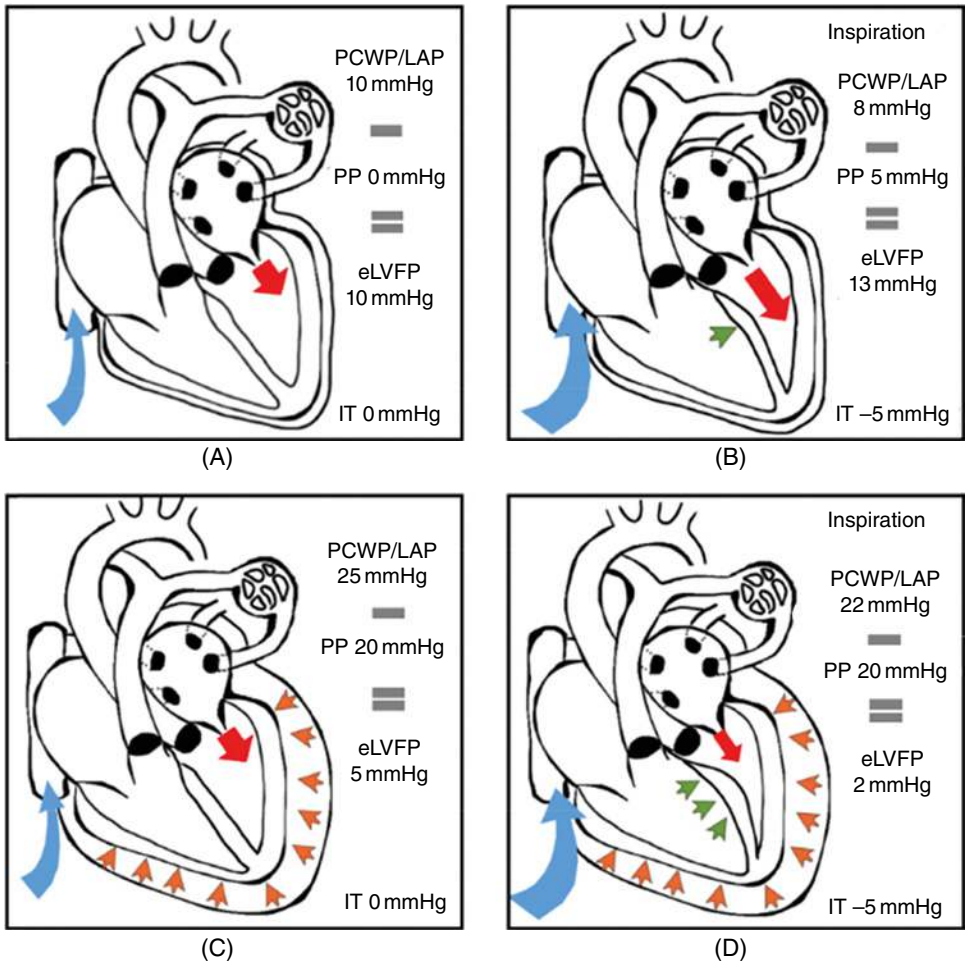


Figure 31.19 Respiratory variation in left ventricular filling. Illustration of effective left ventricular filling pressure (eLVFP) in normal patients at baseline (A) and with inspiration (B) as well as patients with cardiac tamponade at baseline (C) and with inspiration (D). The eLVFP is the difference between the pulmonary capillary wedge pressure (PCWP) or left atrial pressure (LAP) and the pericardial pressure (PP). In normal patients, the PP is low and equal to the intra-thoracic pressure (IT). With inspiration, the PCWP/LAP decreases, and the PP becomes negative, resulting in a net increase in the eLVFP (B). In patients with cardiac tamponade, both the PCWP/LAP are elevated due to the high PP (orange arrows), resulting in a lower eLVFP. With inspiration, there is increased venous return to the right side (blue arrow) and a drop in PCWP/LAP (which lies external to the pericardium) relative to the PP, thus decreasing the eLVFP (D). The LV is consequently restrained both by pressure externally from the pericardium (orange arrows) and internally from interventricular interaction (green arrows). (Source: Vakamudi et al. [68]. Reproduced with permission of Elsevier.)

non-compliance and the pressure increases. Edema of the heart and mediastinal tissues in response to surgery and CPB may greatly decrease the volume and compliance of these spaces. Surgery may also have created continuity of this mediastinal space with the pleural spaces, which will allow large volumes of fluid to be accommodated in the pleura, decreasing the risk of tamponade but allowing greater concealed fluid (sometimes blood) loss. Draining the pleural fluid should also drain the mediastinal fluid in this scenario. In high-risk cases where chest closure is likely to create pressure on cardiac structures or vessels, or closure will create a small non-compliant space, with potential tamponade due to perioperative swelling, delayed chest closure can be used. The sternum is left open, and the skin may be closed directly or by a membrane.

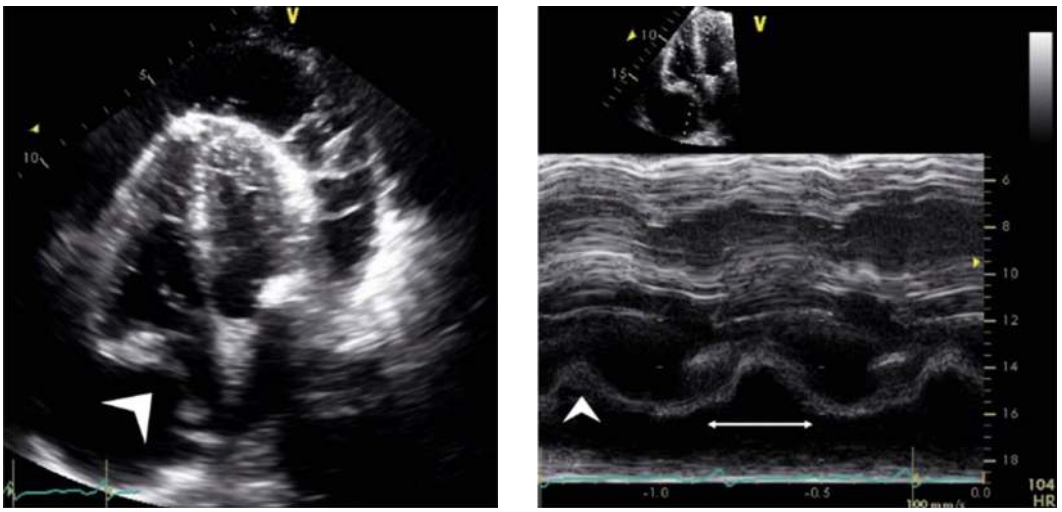
Clinical signs of cardiac tamponade include tachycardia and systemic hypotension and high venous pressure. Beck's triad is the combination of hypotension and high venous pressure (distended neck veins in older children) with quiet sounds on cardiac auscultation [76]. Pulsus paradoxus, which is an exaggeration of the usual minimal (<10 mmHg) decrease in blood pressure with inspiration, increases with the degree of tamponade. Pulsus paradoxus can be quantified during auscultatory measurement of blood pressure by noting the difference between the pressure when the first Korotkoff sounds (which appear during expiration in the spontaneously breathing patient) and the pressure when the sounds become continuous. Other signs of sympathetic activation and low cardiac output, such as cool extremities and pallor from vasoconstriction, may be present. Clinical context will usually give some indication of the origin of cardiac tamponade. Obstruction of mediastinal/pericardial drains may be indicated by tamponade after cessation of previously consistent drainage.

Echocardiography provides a rapid, accurate detailed assessment of pericardial effusions. The site, size, and any evidence of loculation should be evident. This information can inform the selection of the approach to drainage. The degree of myocardial compression and restriction of ventricular end-diastolic volume should also be apparent [77]. Other echocardiographic signs of tamponade physiology include inferior vena cava (IVC) dilation and loss of respiratory variation in diameter of the vessel, right atrial collapse during systole (earliest sign), increase of interventricular dependence with respiration, and respiratory variation of mitral, aortic, or tricuspid inflow peak velocity of >25% [68] (Table 31.9, Figure 31.20). Prompt recognition and urgent treatment of tamponade is critical. In the final sections treatment of tamponade and anesthetic considerations for pericardial disease will be discussed.

Table 31.9 Echocardigraphic features suggestive of cardiac tamponade

Echocardiography Sign	Advantage	Disadvantage
2D and M-mode findings		
RA collapse >1/3 cardiac cycle	Sensitive sign of elevated intra-pericardial pressure.	Difficult to time the duration of collapse. May be confused with normal atrial systole.
RV diastolic collapse	Sensitive sign of elevated intra-pericardial pressure.	Non-specific, may be an early sign of tamponade.
IVC plethora with lack of inspiratory variation	Sensitive sign of cardiac tamponade.	Non-specific, commonly occurs in other conditions associated with elevated central venous pressure.
Doppler flow velocity findings		
PW or CW Doppler assessing variation in tricuspid (>60%) and mitral (>30%) inflow with respiration	Specific finding of cardiac tamponade.	Affected by translational motion of the heart and Doppler alignment. May be absent in patients with elevated left atrial pressure.
Inspiratory decrease and expiratory increase in pulmonary vein diastolic forward flow	Specific finding of cardiac tamponade.	May be absent in patients with elevated left atrial pressure. May be technically difficult to adequately sample the pulmonary vein.
Respiratory variation in ventricular chamber size and aortic outflow velocity	Sensitive finding suggestive of inter-ventricular inter-dependence.	Can also be seen in constrictive pericarditis or other causes of exaggerated changes in intra-thoracic pressure.
PW Doppler of hepatic venous flow velocity showing expiratory decrease or reversal of diastolic flow	High positive and negative predictive values for cardiac tamponade.	Cannot be evaluated in one third of patients due to technical limitations.

Abbreviations: RA = right atrium, RV = right ventricle, IVC = inferior vena cava, PW = pulse wave, CW = continuous wave.
Source: Vakamudi et al. [68]. Reproduced with permission of Elsevier.



(A) (B)

Figure 31.20 Right atrial collapse demonstrated on 2-dimensional echocardiography and M-mode. This figure demonstrates a large circumferential pericardial effusion. On 2-dimensional imaging from the apical four chamber view, there is significant collapse of the right atrium (arrowhead) (A). On M-mode through the right atrium (B), it is clear that the right atrial collapse (arrowhead) occurs during ventricular systole and the duration of collapse is greater than one third of the cardiac cycle (double headed arrow). Source: Vakamudi et al. [68]. Reproduced with permission of Elsevier.

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Surgery for pericardial effusion and cardiac tamponade

Ultrasound-guided, percutaneous drainage of pericardial effusion can be done with local anesthesia, especially in older cooperative patients. A pigtail catheter is recommended to be in place for a day or two when there is a risk of recurrence [78]. In patients in extremis due to tamponade, rapid drainage may be life-saving. If active bleeding is likely to be the source of the tamponade, open operation with surgical control of the bleeding will be required and appropriate maintenance of intravascular volume will be needed. For persistent pericardial effusions, surgical creation of a "pericardial window" by resecting a section of pericardium via an open subxyphoid approach can prevent collection of the fluid in the confined space of the pericardium. For the rare cases of chronic constrictive pericarditis, formal pericardiectomy may be attempted, which is a substantial procedure with the potential for significant complications, such as hemorrhage, arrhythmia, and injury to the coronary arteries. Care must also be taken to avoid puncturing intercostal/ intermammary arteries, the liver, and the lung and using ultrasound guidance may help avoid these structures [78].

Anesthesia for pericardial effusion and cardiac tamponade

Ultrasound-guided drainage of a large pericardial effusion in a minimally symptomatic patient with local anesthesia should be a low-risk procedure, potentially performed without the support of an anesthesiologist. However, there is still the possibility of cardiac perforation or injury to superficial coronary arteries with consequent bleeding or myocardial ischemia. Areas of adhesion between the parietal and visceral layers of the pericardium and loculation of the fluid will increase the risk of these complications. Careful ultrasound assessment and real-time guidance of the tip of the needle should minimize these risks [79].

Patients having anesthesia for surgery to create a pericardial window for persistent effusions require careful assessment for the degree of tamponade present, especially if there is no drain currently in place. Most of these cases will have sufficient reserve to tolerate a careful induction of general anesthesia and institution of positive pressure ventilation. If there is evidence of significant tamponade, staged progress in anesthesia and surgery can be planned. Initial modest doses of sedation and analgesia, combined with local anesthesia, can allow percutaneous drainage of the effusion with relief of tamponade before the initiation of formal general anesthesia and controlled ventilation.

The highest-risk scenario is acute severe cardiac tamponade, usually due to postoperative hemorrhage in pediatric cardiac surgical centers, but also seen in trauma. The patient's condition may be deteriorating rapidly and already be perilous. Rapid intervention is required but induction of anesthesia may precipitate cardiac arrest. A well-coordinated rapid team response is required. The patient's underlying conditions and current status should be assessed. There may be time for resuscitation with intravenous fluids, inotropes, and vasoconstrictors to support the patient until the tamponade can be relieved and also to create some reserve to allow safer induction of anesthesia. If the tamponade is severe and resuscitation has already been attempted, the highest priority is facilitating rapid relief of the tamponade. The operating room team should be scrubbed and ready to proceed prior to anesthesia is induced. Blood for transfusion should be available and an appropriate anesthesiology team should be in place. If further intravenous access and (if the patient is stable enough) intra-arterial access is to be gained, multiple anesthesiologists/assistants may allow efficient and safe preparation of the patient. Induction of anesthesia can cause cardiovascular collapse by direct cardiac depression and vasodilation, as well as by decreasing the central sympathetic outflow. Even drugs with minimal direct depressive effects, such as fentanyl, can have a profound effect by this latter mechanism. Synthetic opioids are also prone to decreasing heart rate, which will also jeopardize circulation. Positive pressure ventilation will exacerbate the problems with venous return and compression of the heart that have been created by the tamponade, increasing the chance of circulatory collapse.

The anesthesia sequence in these cases of severe tamponade needs to be tailored to the patient's circumstances. Coagulopathy is a serious consideration in these patients and an INR above 1.5 or a platelet count of less than 50,000 is considered a relative contraindication for pericardiocentesis and may require urgent correction with platelets or clotting factors [74]. Fasting status should be considered and cricoid pressure may be implemented, even if other parts of rapid-sequence induction and intubation are modified due to the risk of circulatory collapse. The possibility of major surgical procedures to remedy the cause for bleeding once the tamponade is relieved should be considered. It may be appropriate to initially drain the pericardium with minimal sedation and analgesia and local anesthetic, which may improve cardiovascular reserve and allow safer induction of anesthesia. Anesthesia induction should be done with low doses of agents that are least likely to decrease sympathetic drive, such as ketamine (despite its potential for direct myocardial depression) titrated slowly, as the central circulation will be small and excess anesthesia effect should be minimized. Drainage of the pericardium before intubation and the introduction of positive pressure ventilation should be considered. When positive pressure ventilation is introduced, providing a substantial expiratory time with minimal or no positive end-expiratory pressure should minimize impairment of venous return. Once the pericardium is drained, hemodynamic stability will usually be rapidly restored. In postoperative tamponade, often an active bleeding point may be easily controlled, such as from the site of an intracardiac catheter that had been removed, but occasionally the hemorrhage will be from a major suture line that is now bleeding vigorously, with an increase in blood pressure and loss of tamponade. This may require ongoing resuscitation and major surgical intervention, including CPB, to revise the surgery.

In the cardiac catheterization laboratory, the heart or the great vessels may be perforated by a catheter or wire, which may result in acute severe cardiac tamponade, diagnosed by angiography or echocardiography demonstrating the blood in the pericardial space. Many of these patients will already be under deep sedation, or intubated general anesthesia. In addition to intravascular volume infusion and resuscitation

drugs, the cardiologist must drain the pericardial space immediately; this is non-clotting blood and can be reinfused directly into the patient via a three-way stopcock. The femoral venous sheath is the preferred route of reinfusion but the anesthesiologist can utilize other appropriately sized intravenous access. This maneuver can be life-saving as preparations are made for sternotomy and repair of the perforation [80](Figure 31.21).

In postoperative patients in the intensive care unit with circulatory collapse secondary to cardiac tamponade, rapid reopening of the sternum in the unit may be life-saving.

KEY POINTS: ANESTHESIA FOR CARDIAC TAMPONADE

- Cardiac tamponade is associated with high venous pressures, tachycardia, and systemic hypotension and may be life-threatening without emergent treatment
- Before anesthesia is induced, the operating room team should be in place and ready to proceed with rapid surgical relief of the tamponade.
- Local anesthesia, with minimal or no sedation and analgesia, and ultrasound-guided drainage may be the safest option and help avoid puncturing important structures
- If greater levels of sedation analgesia or anesthesia are required, slow titration and agents with less sympatholytic action should be used. Initial surgical drainage may be performed with spontaneous ventilation prior to endotracheal intubation.
- Avoiding positive pressure ventilation until the pericardium is drained may avoid circulatory collapse.

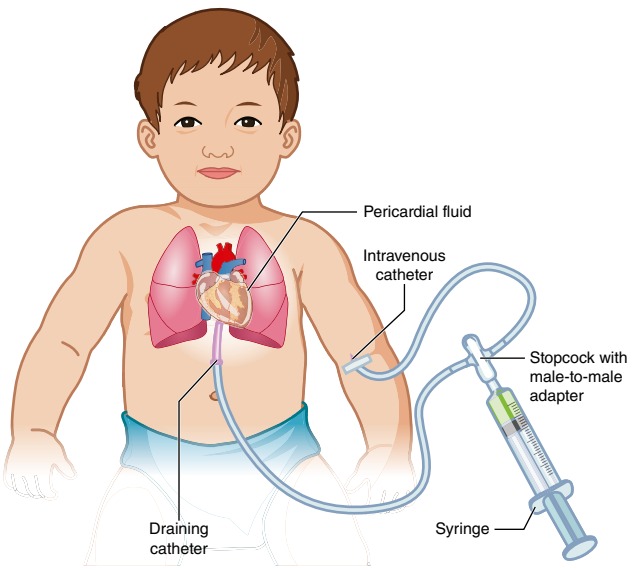


Figure 31.21 Drainage and retransfusion system for acute pericardial tamponade for cardiac perforation in the catheterization laboratory. The femoral venous sheath, if available, is the preferred site for reinfusion of blood. (Source: Mossad [80]. Reproduced with permission of Elsevier.)

Mitral regurgitation

Incidence, anatomy, and natural history of mitral regurgitation

Isolated mitral regurgitation (MR) is an uncommon pathology in childhood. The atrioventricular valve serving the systemic ventricle is not considered a mitral valve in the relatively common atrioventricular septal defect, univentricular hearts and in patients with "congenitally corrected transposition of the great arteries" (i.e., combined atrioventricular and ventriculoarterial discordance). Abnormalities of these "non-mitral" left atrioventricular valves are discussed in the relevant chapters (see Chapters 26, 29 and 30 for further discussion).

Normal anatomy and function of the mitral valve

The normal mitral valve allows low resistance passage of blood from the left atrium to the left ventricle during ventricular diastole and prevents blood from returning from the left ventricle to the left atrium during ventricular systole. Abnormalities of the valve can result in restriction of forwarding flow (stenosis) or the return of blood from the left ventricle to the left atrium during ventricular systole (regurgitation or incompetence). MR and stenosis may occur in combination [81] (Figure 31.22).

The mitral valve consists of an annulus, two leaflets, three types of chordae, and two dominant papillary muscles, as shown in Figure 31.23 [82]. The annulus is part of the continuous fibrous framework separating the atria and ventricles. There are two mitral valve leaflets: anterior and posterior. The leaflets are not symmetrical. The posterior (mural) leaflet is attached to 210 degrees of the circumference of the annulus, where it is continuous with the left ventricular free wall. The annulus is also in continuity with the aortic valve through the fibrous aortic-mitral curtain. The anterior (septal) leaflet is attached to the portion of the ring continuously with the septum and aortic valve over about 150 degrees. The anterior surface of the anterior leaflet is thus the posterior surface of part of the left ventricular outflow. On the closure of the mitral valve, the posterior leaflet forms a crescentic ("C"-shaped) part of the closure of the annulus, contributing only about a third of the cross-section of the closure despite the whole leaflet being much larger than the anterior leaflet. The smaller anterior leaflet contributes the remaining, more oval, two thirds of the closure of the annulus. This arrangement of the valve leaflets means that the posterior leaflet leaves little space between the free wall and the leaflet during systole and the anterior leaflet moves towards the posterior leaflet, increasing the diameter of the left ventricular outflow during systole. The crescentic portion of the posterior valve and the oval portion of the anterior valve, which close off the annulus, are a relatively small proportion of the total surface area of the valves. During mitral valve closure, a significant proportion of the surface area of the valves leans on each other, thus providing "mutual support" during closure. This coaptation of the valve leaflets decreases tension in the valve tissue required to maintain valve closure. The valve leaflets have multiple fibrous bands, chordae tendinae,

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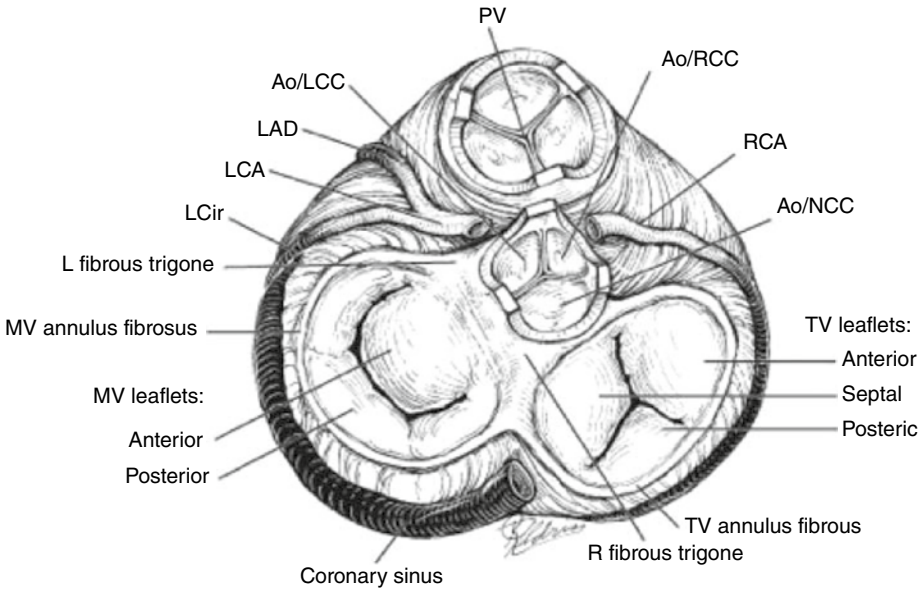


Figure 31.22 Cross-sectional drawing of the heart showing the anatomic relations of the normal mitral valve. Ao/ LCC, aortic valve left coronary cusp; Ao/ NCC, aortic valve non-coronary cusp; Ao/ RCC, aortic valve right coronary cusp; L, left; LAD, left anterior descending coronary artery; LCA, left coronary artery; LCir, left circumflex coronary artery; MV, mitral valve; PV, pulmonary valve; R, right; RCA, right coronary artery; TV, tricuspid valve. (Source: Mainwaring & Lamberti [81]. Reproduced with permission of John Wiley & Sons.)

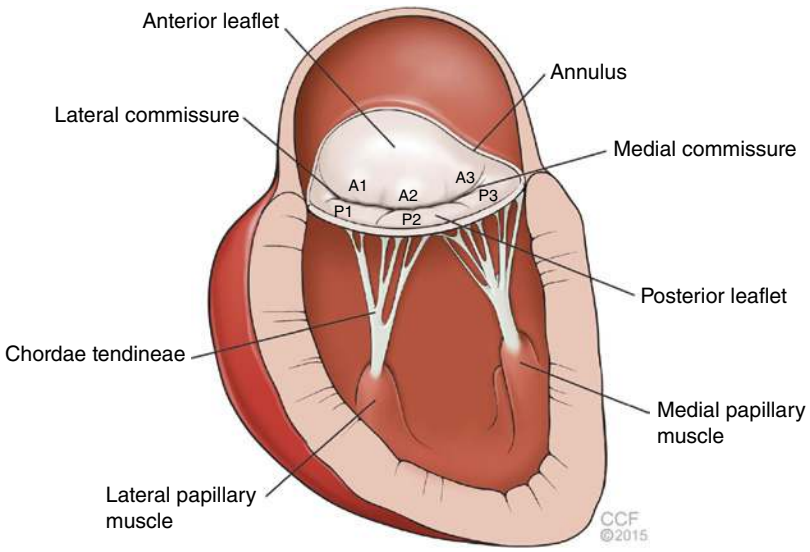


Figure 31.23 Mitral valve anatomy. The mitral valve apparatus is shown here with the annulus, leaflets, chordae tendineae, and papillary muscles. Each leaflet anterior (A) and posterior (P) is divided into three scallops (1 for lateral, 2 for middle, and 3 for medial). (Source: Harb and Griffin [82]. Cleveland Clinic Center for Medical Art & Photography © 2017. All Rights Reserved.)

which connect them to both the papillary muscles (anterior and posterior), projecting from the inner wall of the mid-left ventricle. The posteromedial papillary muscle has a single blood supply from the posterior descending artery while the anterolateral papillary muscle is usually supplied by both the left anterior descending and the left circumflex. The chordae connect to both the surface and edge of the valve leaflets, distributing the forces of systolic papillary muscle contraction over a wide area of the valve leaflets [83].

Classification of mitral regurgitation

The two broad categories of MR are primary and secondary. Primary MR is a degenerative valvular disease usually caused by leaflet prolapse or flail. Secondary MR, also known as *functional* MR is a heterogenous group of conditions that refer to abnormalities of the systolic tethering of the mitral valve apparatus caused by abnormal left ventricle size, shape, or function. Therefore, therapy is focused on the restoration of LV structure and function rather than mechanical

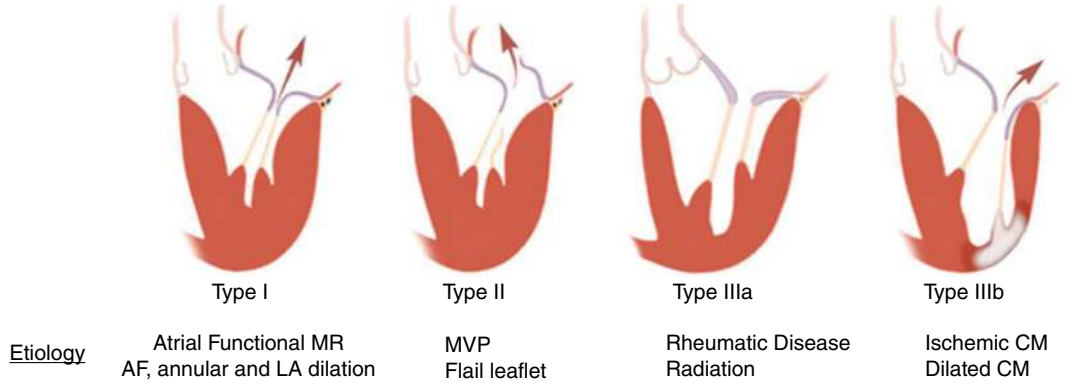


Figure 31.24 Carpentier classification. The Carpentier Classification defines mitral regurgitation (MR) in relation to mitral leaflet motion. Type I signifies normal motion (as in atrial functional MR), type II excessive motion (prolapse/flail) and Type III restricted motion (secondary MR due to underlying cardiomyopathy. (Source: Adapted from Harb & Griffin [82].)

interventions to reduce the MR. Some examples of this therapy are neurohumoral antagonists and resynchronization devices. Questions remain on whether therapy that targets *only* the mitral valve will benefit some of these patients with secondary MR. [84] The Carpentier Classification categorizes MR on the basis of leaflet mobility. Those with secondary MR usually fall into Carpentier Class 3B [85] (Figure 31.24).

Quantifying regurgitant volume is important. Consensus defines *severe* MR as a regurgitant fraction of over 50%, that is, over half of the total stroke volume is directed backwards into the left atrium instead of forward into the aorta. One way of measuring this severity on echocardiography is with the effective regurgitant orifice area or EROA [86]. Unfortunately, the EROA is highly dependent on left ventricular volume (LVEDV), pressure (LVEDV), and function and has significant interobserver disagreement; thus, its reliability has been questioned [84].

Grayburn and colleagues have proposed a new conceptual framework for categorizing secondary (functional) MR as either *proportionate* or *disproportionate* [87]. The principal reason for this is to determine whether interventions directed at the mitral valve can change the clinical course of the disease. In their view, it is important to determine whether the estimated degree of MR is expected or *proportionate* to the degree of LV dilation, or alternatively, whether the severity of MR is unexpected, or *disproportionate* to the degree of LV enlargement. A patient whose MR severity is consistent with their amount of LV dilation (proportionate MR) might not be expected to improve following a valve intervention. On the other hand, a large degree of MR relative to the degree of LV dilation (disproportionate) might respond favorably [87].

Two randomized control trials, MITRA-FR [88] and COAPT [89] support Grayburn's proposed framework. In the French MITRA-FR trial, 307 patients with secondary MR underwent transcatheter MV repair. The patients enrolled showed striking degrees of LV dilation and *proportionate* degrees of MR. These patients at analysis showed no improvement in LV volume after one year of valve repair. In contrast, the U.S.-Canadian COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR) randomized 614 patients to undergo transcatheter MV repair or control. Contrary to the MITRA-FR study, valve repair in this group led to a significant reduction in LV volume at follow-up. The enrolled COAPT patients had MR that was *disproportionately* greater than their degree of chamber enlargement. When COAPT patients are compared to MITRA-FR patients, as a group, the COAPT patients had EROA values 30% *higher* but LV volumes 30% *smaller* [84].

This framework suggests that distinct secondary MR patient subgroups patients will likely benefit from *different* types of medical treatments or valve-directed therapies. Disproportionate MR patients respond poorly to neurohumoral antagonists traditionally prescribed for associated cardiomyopathy but benefit more selectively from interventions that are directed toward restoring valve function such as valve repair/replacement or cardiac resynchronization therapy (CRT). Distinguishing these different types of MR patients is important since the *proportionate* patients have valve disease that can be explained by their degree of LV dilation and thus respond better to neurohumoral antagonist therapies.

Mechanisms of mitral valve regurgitation

Abnormalities of the annulus, leaflets, chordae, or papillary muscles may be associated with MR. Conditions that volume load the left ventricle, such as aortic regurgitation and heart failure with eccentric left ventricular hypertrophy (e.g., dilated cardiomyopathy), may cause annular dilation. Dilation of the annulus increases the area requiring closure and decreases the area of leaflet available for coaptation, both of which increase the mechanical stress on the valve tissue during systole, which may lead to immediate failure of coaptation and regurgitation or valve prolapse (see later) with subsequent regurgitation. A cleft in the annulus may not be able to be sealed by the leaflet tissue [90, 91].

Mitral valve leaflet distension, cleft, or restriction may lead to regurgitation. Distension of the valve, which may result from congenital structural abnormalities or may develop due to connective tissue disorders (e.g., Marfan syndrome) or inflammatory conditions such as rheumatic fever, can cause a portion of the valve to balloon beyond the plane of the annulus during valve closure (i.e., prolapse). This

prolapsed portion is no longer supported by the opposing valve and, as with aneurysms, the law of Laplace will apply, and wall tension will rise as the prolapse progresses and tend to make that region expand until the valve fails to oppose or even ruptures. Restriction of leaflet movement, such as with fibrosis due to inflammation, may prevent a leaflet from coapting with the opposing leaflet and consequent regurgitation. Similarly, elongation of the chordae may cause leaflet prolapse while shortening, and fibrosis may cause restriction of leaflet movement, with regurgitation developing in both scenarios. Rupture of chordae may cause acute regurgitation. Acute MR when it occurs is often a medical *and* surgical emergency. Patients usually present with severe dyspnea, decompensated heart failure, and/or severe pulmonary edema due to the sudden pressure and volume load imposed on a previously normal left atrium [92]. Fibrosis of either leaflets or chordae also tends to be associated with stenosis of the valve. Elongation of papillary muscle can cause valve prolapse and regurgitation of the mitral valve. Papillary muscle dysfunction may also cause MR. For example, in dilated cardiomyopathy, poor contraction and elongation of the papillary muscles and consequent leaflet prolapse will often be exacerbated by annular dilation and cause marked MR. Specific papillary muscle dysfunction can arise in relation to coronary artery problems, as the blood supply of the papillary muscles is usually from separate coronary arteries. Mistiming of papillary contraction in relation to the rest of ventricular contraction may be associated with MR. This may occur with some abnormalities of the coordination of the timing of regional contraction, such as conduction disturbances, some arrhythmias and complications of the pacing of the ventricle. Other rare causes of MR include distortion of the valve apparatus due to tumors [49].

Many of the conditions associated with MR can affect multiple areas of the valve apparatus (annulus, leaflets, chordae, papillary muscles) and compound the problem. Fusion of the valve leaflets at the commissures is usually associated with stenosis rather than regurgitation.

In adults, the commonest mechanism of MR is mitral valve prolapse, which is usually asymptomatic and often presents incidentally with an auscultatory click and murmur. The earliest phase of this may be "superior systolic motion" of mitral leaflet tissue above the plane of the annulus. In clinically normal children, this echocardiographic sign increases in frequency from around 1% in infants to nearly a quarter of 6- to 10-year-olds and more than a third of 11- to 18-year-olds. Some of these cases may progress to prolapse and significant regurgitation, but, given the benign outcome in most, isolated superior systolic motion is usually considered a variation of normal.

Rheumatic cardiac disease is common on a world scale and, although appearing sporadically in a wide range of communities, is commonest in socioeconomically disadvantaged communities with a high incidence of streptococcal infection and poor general health. It is the most common cause of mitral valve *stenosis* worldwide. The highest incidence of rheumatic fever in the world is said to be in the indigenous communities of remote Australia. MR is the commonest rheumatic valve lesion in children with this condition, with mitral stenosis appearing later in the disease progression, and involvement of other valves, such as the aortic, being less common initially. Public health measures for the prevention of rheumatic fever are the most important long-term approach. Valve-preserving reconstructive surgery has a number of advantages for children with rheumatic MR, avoiding the need for replacing an artificial valve due to growth and the need for anticoagulation (which may be difficult to manage in many of the communities with the highest incidence of rheumatic fever).

MR tends to be a progressive condition, as the regurgitation volume loads the left ventricle, which will dilate, exacerbating the regurgitation. Children who have a successful surgical repair of MR tend to have recovery of ventricular function and good long-term outcomes. There is an association between the long-term presence of regurgitation and atrial arrhythmias, which may continue or arise after repair. This is associated with chronic enlargement of the left atrium, which may be addressed in high-risk cases at the time of surgical intervention for the regurgitation.

Pathophysiology of MR

MR will tend to worsen with time unless the underlying pathology is corrected. The presence of regurgitation results in the need for bigger end-diastolic volumes if an adequate forward flow (cardiac output) is to be maintained as well as accommodating the regurgitant fraction, which returns through the mitral valve during systole. Increased left ventricular end-diastolic volume (LVEDV) will promote dilation of the annulus which will tend to increase the regurgitant fraction, thus creating a disadvantageous positive feedback loop of increasing regurgitation and dilation of the left ventricle, until ventricular dysfunction is superimposed on the process, which will result in decompensation of the cardiovascular system.

MR is exacerbated by factors that increase left ventricular afterload and volume loading. Lessening SVR and relieving aortic valvular abnormalities (either stenotic or regurgitant) will tend to decrease MR. If myocardial ischemia is contributing to papillary muscle dysfunction, this may be resolved by restoring coronary artery blood flow. In some cases, MR can resolve without mitral valve surgery, if the underlying precipitating factors are resolved. The onset of atrial arrhythmias, such as atrial fibrillation, associated with left atrial dilation due to MR, may trigger cardiovascular decompensation. Persistent severe MR, especially in association with the onset of ventricular dysfunction and the associated very high left ventricular end-diastolic pressures, may cause significant pulmonary hypertension with impairment of right ventricular function. The right ventricular function may also be impaired by the dilation of the left ventricle, which causes a ventricular septal shift toward the right ventricle.

Surgical approaches and outcomes for MR in children

The advent of high-quality echocardiography, including 3D imaging of the mitral valve, has contributed greatly to the understanding of the mechanisms of MR. Surgical repair can now address all levels of factors contributing to regurgitation [93].

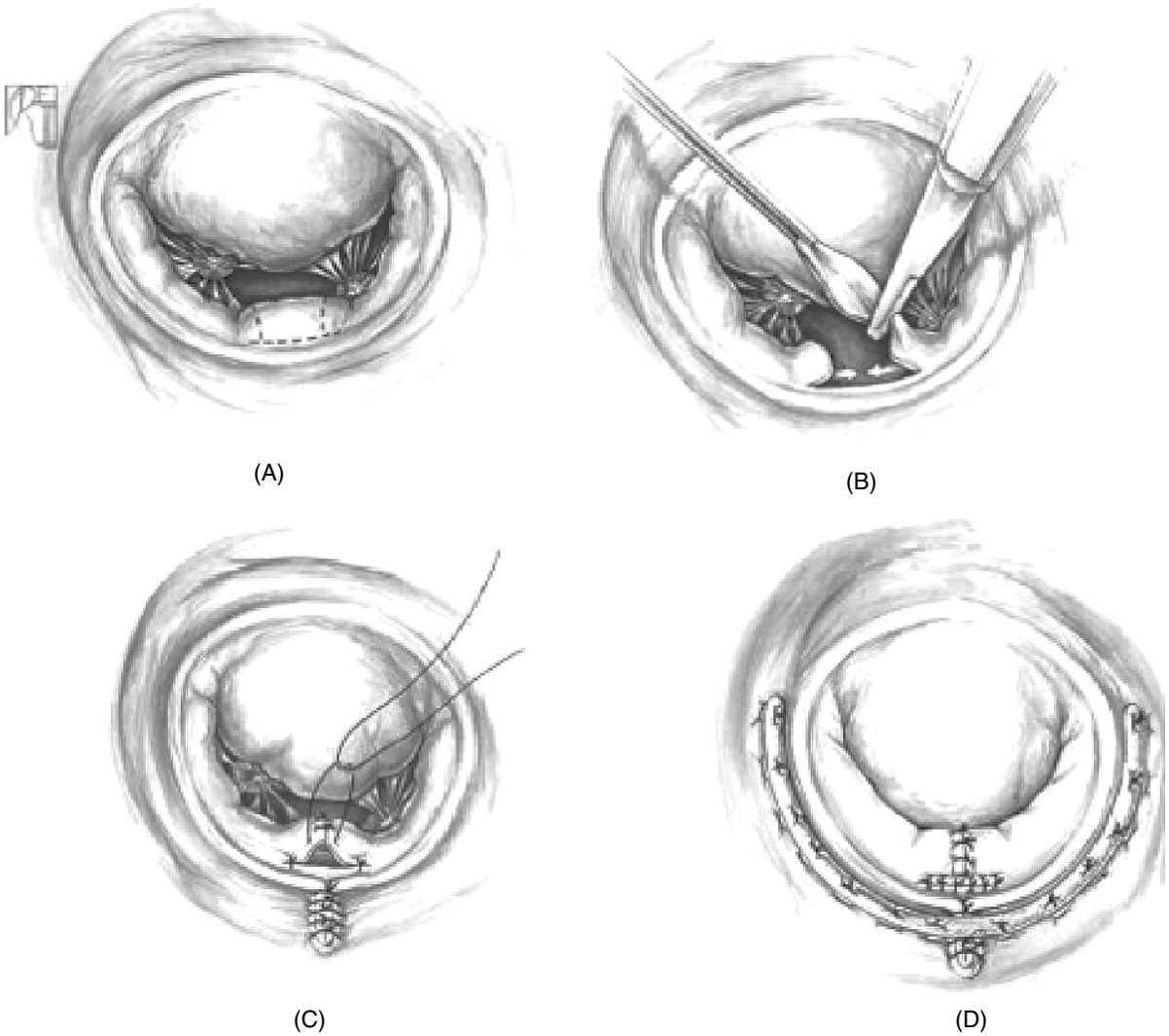


Figure 31.25 (A) Insufficient mitral valve due to annular dilatation. Dotted lines represent the proposed posterior leaflet quadrangular resection and valvular incisions. (B) After quadrangular resection, linear incisions are made in the posterior leaflet to accomplish sliding valvuloplasty (arrows). (C) The posterior annulus is brought together with care not to injure the circumflex coronary artery. Resultant tightening of the annulus brings the remaining scallops of the posterior leaflet into position for valvular repair. (D) The repair is strengthened by a semicircular Gore-Tex® strip. The anterior annulus was not included in the annuloplasty technique to allow for somatic growth. (Source: Mainwaring & Lamberti [81]. Reproduced with permission of John Wiley & Sons.)

Thus the annulus can be supported or decreased in size with a number of techniques, including insertion of a supravalvular ring [81] (Figure 31.25). The leaflets can be modified to prevent prolapse and have patches inserted and fibrotic areas debulked, thus improving coaptation and movement. Fusion of commissures where valve leaflets have joined may need to be freed to allow adequate valve movement and to relieve stenosis, but a more complex repair may be required if commissurotomy creates a cleft or failure of coaptation. Chordae can be reimplanted or changed in length, and papillary muscle elongation shortened. The aim of avoiding valve replacement is realistic for most pediatric cases. Mitral valve replacement has higher long-term mortality than any other valve replacement in children; infant mitral valve operative mortality has been reported to be 5–52%, and 5- and 10-year survival rates to be 33–95% [94]. The benefits of valve repair over replacement include avoiding the need for anticoagulation, the need for replacement of the artificial valve with growth in smaller children, and the high risk of mitral valve replacement in babies. In this last group, there is a lack of very suitable artificial valves and the surgery is complicated, as the artificial valve ring may need to sit above the annulus and the body of the artificial valve may still impair ventricular function. Bioprosthetic valves may avoid the need for anticoagulation necessitated by mechanical valves but structurally deteriorate over time (often within 2.5–5 years) and can be difficult to obtain in small sizes [95]. The lack of papillary muscle connection to the artificial valve is also associated with an abnormal geometry of ventricular contraction, which may contribute to worsening ventricular function. An individualized patient-centered approach based on underlying anatomy, valve pathology, and patient size with an

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understanding that re-do surgery is inevitable in infants and small children to upsize the prosthesis is fundamental and can lead to successful long-term outcomes and excellent survival [96]. Complex valve repairs have been enabled by modern techniques for myocardial preservation that allow long cross-clamp times to be well tolerated with good postoperative myocardial function.

For children with underlying conditions, which may continue or recur, such as connective tissue disease or rheumatic fever, there is a significant risk of recurrence of MR. Time gained in growth before an artificial valve is required is often a great advantage, and repeated surgery for repair of the native valve may still be a reasonable management plan in children.

Transcatheter percutaneous approaches to mitral valve repair have been established as a safe and less invasive alternative to open surgical MV repair. One such device, the Mitra-Clip® (Abbott Vascular, Menlo Park, CA) was modeled after the surgical Alfieri stitch which is the application of a suture at the site of the regurgitant jet, between the anterior and posterior leaflets (usually A2 and P2), creating a "double-orifice" valve without residual prolapse and overall less regurgitation (Figure 31.26). The Mitraclip percutaneous "edge to edge" transcatheter clip technique has been shown in numerous adult clinical trials to be safe and effective. Transcatheter techniques are the natural evolution of modern valve surgery but this technology in pediatrics is still in early clinical stages. Some novel devices and xtremely, such as transcatheter valve in valve insertion, chordae reimplantation, and catheter-based annuloplasty, are currently under development [97]. Pediatric transcatheter techniques pose many obstacles such as device durability, limited device sizes, and the potential need for future procedures with somatic growth and development. The MitraClip for example has an xtremely large 24 French introducer sheath which requires a minimum patient age of about 9–12 years with a minimum weight of approximately 40–45 kg [97, 98]. Although large studies are lacking there have been successful cases of transcatheter MV repair in pediatric patients utilizing both the MitraClip [98] and also the Melody Valve (Medtronic, Inc. Minneapolis, MN), a stented bovine jugular vein graft, commonly used in the pulmonary valve position. The Melody offers the advantage that it can be balloon dilated as a child grows [99]. It has even been modified for use as a surgical implant [100, 101] (Figure 31.27). This allows the option of future transcatheter balloon dilation from a starting size of 12 mm up to 22 mm, the size of an adolescent mitral valve. The procedure requires a fenestrated atrial septum to facilitate future dilations and reported complications include LV outflow obstruction, acute mitral regurgitation or stenosis, left circumflex coronary compression, acute distal obstruction of the valve from stent deformation, and transient complete heart block [101]. Further study is needed to determine the viability and the long-term durability and safety of this device [100, 102].

Surgery is best timed before there is severe chronic dilation of the left ventricle with loss of function, although follow-up studies in children suggest that successful repair is associated with good recovery of function over the long term. Chronic left atrial dilation is associated with atrial arrhythmias, which may persist or commence postoperatively.

Anesthetic considerations for the repair of MR

Functional assessment of the MR is based on the history of activity and exercise tolerance and is a robust measure of cardiorespiratory reserve. In infants, cardiac failure may be indicated by breathlessness and sweating with feeding, and poor weight gain. Physical examination should not only elicit the pansystolic murmur typical of MR but also seek signs of complications such as an enlarged left ventricle, or cardiac failure with a third heart sound and evidence of pulmonary congestion. History and examination may also indicate underlying conditions that may have caused the MR, such as rheumatic fever or Marfan syndrome, as well as signs of other associated cardiac lesions. Echocardiography can provide information about the severity of the regurgitation, associated lesions, and myocardial function [103]. Understanding the mechanism for the regurgitation is crucial for planning the surgical approach to repair. Standard "adult" echocardiographic measures to quantify MR may not be applicable to small pediatric patients and assessment of the severity may require interpretation rather than being able to be precisely quantified. Factors include the diameter of the base of the regurgitant jet, the shape and distance that the regurgitant plume penetrates into the left atrium, whether there is retrograde flow generated in the pulmonary veins and left atrial dilation as well as estimates of the regurgitant fraction (compared with total ejection of the ventricle). Standard estimates of myocardial function may be difficult to interpret in the presence of a dilated ventricle. The increase in volume that occurs with ventricular dilation, proportional to the third power of the diameter, means that a greater volume change occurs with a change in diameter at larger diameters. Therefore, when the dilated ventricle is full, the change in volume with contraction is very much larger than the change in volume caused by a similar decrease in diameter at a smaller starting volume. Thus, apparently small movements of the dilated ventricle may be associated with substantial volumes of ejection. Measures of tissue acceleration or initial rate of change of pressure over time may reflect underlying myocardial function better than measures of ejection fraction. Measures of ejection fraction are also complicated by the fact that there are separate "forward flow" and regurgitant fractions and that the regurgitant fraction can be considered a low resistance pathway and decreases the afterload of the ventricle (this "afterload" reduction arising from the retrograde regurgitant flow). The presence of this low-resistance pathway may also influence functional measures of contraction, in that the rate of contraction may be increased compared with ejection into a higher resistance system.

Patient management up to the time of presentation should also be assessed. Medical therapy for MR with systemic vasodilators such as angiotensin-converting enzyme inhibitors can decrease the regurgitant fraction. Systemic vasodilation will change the balance in favor of "forward flow" compared with regurgitation. Systemic vasodilation, often aided by diuretic therapy, can decrease end-diastolic ventricular volume, which may further reduce regurgitation by decreasing the size of the annulus. Improvements in echocardiographic measures of MR have been noted after the first dose of captopril. Optimizing medical therapy and nutrition should

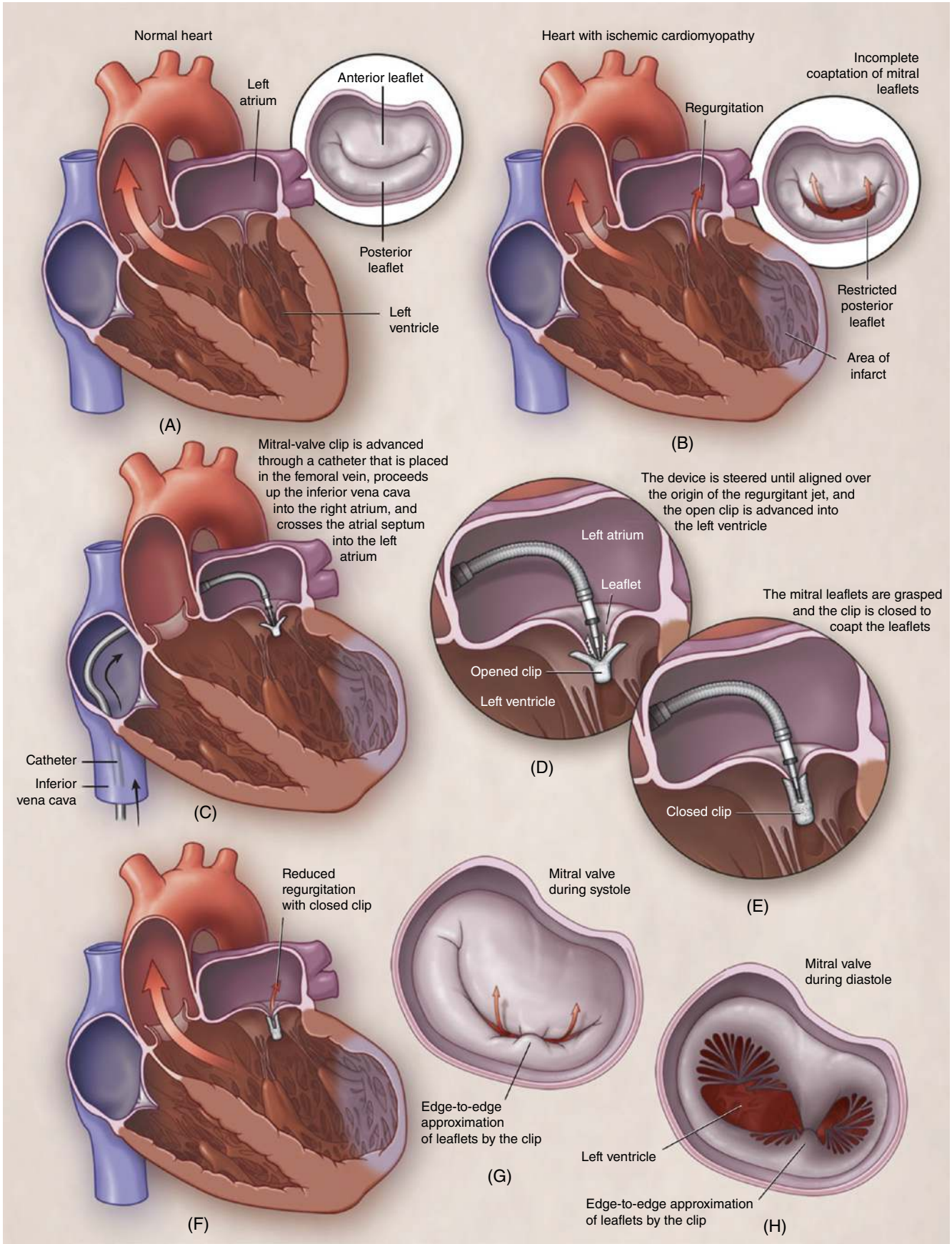


Figure 31.26 Mitral clip insertion for mitral regurgitation. (Source: O'Gara & Mack [85]. Reproduced with permission of Massachusetts Medical Society.)

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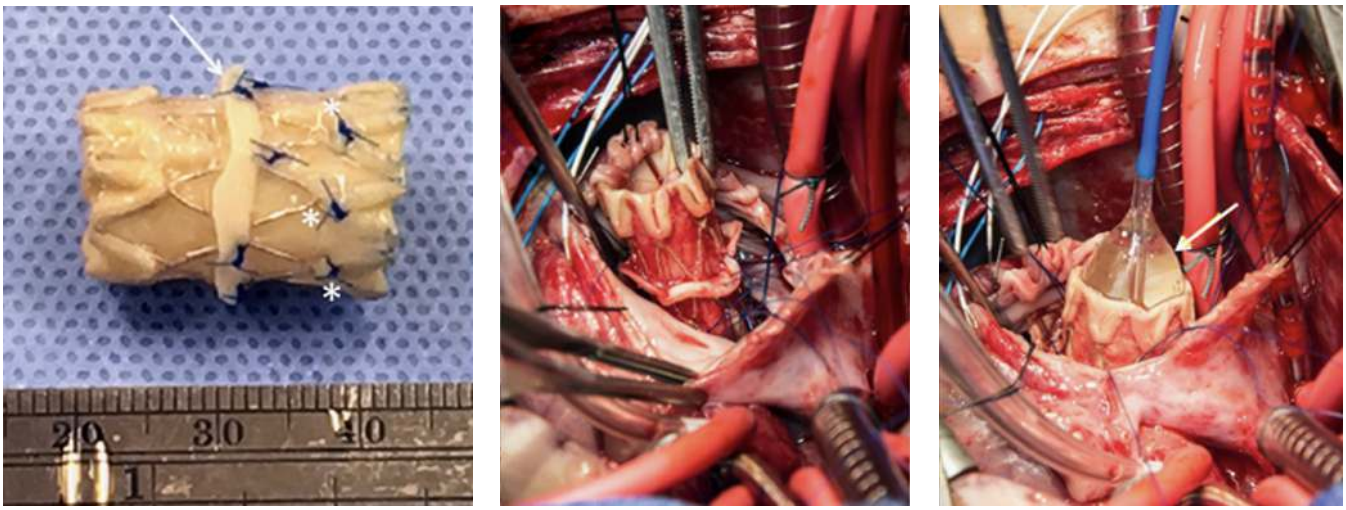


Figure 31.27 (A) Modified Melody valve prepared for implantation. The terminal crowns were folded back on both ends to lie flat against the stent and the anterior folded crowns were stitched down to prevent protrusion into the left ventricular outflow tract (LVOT) upon further expansion (*). A pericardial cuff is sewn into place to secure the valve onto the mitral annulus (*arrow*). (B) The valve is implanted, secured onto the annulus and the distal end stitched to the posterior left ventricular wall to avoid LVOT obstruction, and (C) dilated using a 12 mm balloon (*arrow*). (Source: Sullivan et al. [101]. Reproduced with permission of Cambridge University Press.)

provide more cardiorespiratory reserve for the patient at the time of surgery.

In patients with MR and well-preserved myocardial function, anesthesia is usually well tolerated. Anesthesia induction should avoid increases in SVR. Increased SVR will increase the regurgitant fraction and jeopardize forward flow. Heart rate should be maintained, as the increased LVEDV associated with bradycardia will worsen MR. Excessive intravascular volume loading may also worsen MR by increasing LVEDV and distending the annulus. Positive pressure ventilation and PEEP should improve respiratory mechanics by decreasing lung congestion and optimizing functional residual volume. Cardiovascular performance should also be favorably influenced, as positive pressure ventilation will tend to increase left atrial pressure and decrease the afterload of the left ventricle, both of which should improve cardiovascular performance in patients with MR.

Monitoring should be as for any pediatric CPB procedure. In patients with severe MR and cardiac dysfunction, surgically placed pulmonary artery and left atrial lines may be warranted for the post-repair phase. TEE is very helpful in both planning and assessing the surgical repair, but it can also be a useful monitor to inform decisions about strategies to support the cardiovascular system.

In late presentations of MR, with myocardial dysfunction and pulmonary hypertension, or patients with associated lesions such as mitral stenosis, the risk of cardiovascular decompensation with anesthesia is greater. Apart from having less reserve, some conditions may do better with an opposite strategy to that which is optimal for MR. For example, maintaining, and even increasing, SVR will benefit patients with mitral stenosis, whereas decreasing SVR is an aim for patients with MR. The more severe the cardiovascular disease and the more complex the associated conditions, the more tightly the circulation should be monitored, and titration of anesthesia drugs, cardiovascular agents, and ventilation strategies should be constant to maintain a stable circulation. In pure MR with cardiovascular decompensation, an inodilator such as milrinone or low-dose dobutamine may be useful to provide both low SVR and improved contractility.

Most cases with isolated MR and preserved myocardial function who have successful repair of the lesion and high-quality myocardial preservation during the aortic cross-clamp phase will tolerate the procedure well and are likely to be candidates for early extubation after the procedure. The commonest issue with these patients in the postoperative phase is that the good function with a dilated left ventricle creates an almost obligatory large stroke volume, which may create significant systemic hypertension. Systemic vasodilation and avoiding tachycardia may be indicated. Appropriate sedation and analgesia will assist these aims. Centrally acting α_2-adrenergic agents such as clonidine or dexmedetomidine may be useful supplements in this phase, contributing to sedation, analgesia, systemic vasodilation, and a tendency to a low heart rate. More complex cases with poor function and associated lesions or residual valve lesions will usually require more support and a longer intensive care course.

Patients with poor function and residual regurgitation in the early postoperative phase may have a decrease in the regurgitation as function improves. This may relate to decreasing ventricular dimensions with improved function, which decreases the size of the annulus, and to improvement in papillary muscle function, stabilizing the leaflets and decreasing prolapse. This may influence the judgment of when an immediate revision of the repair is indicated when the intraoperative post-bypass echocardiography demonstrates residual regurgitation. This judgment is also informed by the mechanism of the residual regurgitation, as some mechanisms may be clearly mechanical (rather than

"dynamic"), reparable with further surgery, and unlikely to improve without surgical intervention.

Catheter-based therapy for the treatment of valvular heart disease was developed for aortic and pulmonary valves in the early 2000s and significantly altered the care of this population [104]. Transcatheter mitral valve interventions have been a natural evolution of this technology. Though less invasive than sternotomy and cardiopulmonary bypass procedures, these surgeries pose unique anesthetic risks, especially in their more austerely monitored environment. General endotracheal anesthesia with TEE guidance is the norm. The mitral valve sits in close apposition to the LVOT and reported complications previously mentioned can be clinically significant. In addition, hybrid surgical strategies involving combined cardiosurgical and interventional approaches have been used for other congenital lesions and are currently under investigation for mitral valve procedures [105]. Having intraoperative and postoperative strategies for managing life-threatening arrhythmias, bleeding, or hemodynamic compromise is a critical part of the anesthetic plan in these minimally invasive cases.

KEY POINTS: ANESTHESIA FOR MR

- Isolated MR is uncommon in childhood.
- Associated conditions such as rheumatic fever or connective tissue disorders and other valve lesions should be sought.
- Repair rather than replacement of the valve is the usual aim in childhood.
- Pre-bypass, anesthesia techniques should aim to avoid increases in SVR and bradycardia, which will both increase the regurgitant fraction.
  - Transcatheter mitral valve repair techniques have a good safety record in adults. Successful use in children has been demonstrated but large studies in the pediatric population are lacking. Vigilance for anticipating serious but rare complications during minimally invasive catheter-based valve procedures must be maintained.

Cardiac tumors in childhood

Incidence, anatomy, and natural history

Cardiac tumors in children are rare, with the quoted incidence in the literature anywhere from 0.01 to 0.4% depending on the series and the particular population studied [106]. In a review of 14,000 fetal scans, the incidence of the cardiac tumor was 1.4/1,000 patients [107]. Depending on the definition used, any mass in the heart can be described as a tumor. This discussion will exclude thrombus, vegetations, and other inflammatory masses, but it is important to consider these in the differential diagnosis of a mass under investigation.

Cardiac tumors in children are almost all benign with malignant tumors comprising only a small proportion, including metastases from primary tumors elsewhere. The cardiac anesthesiologist may also see patients with tumors arising in remote tissues that have grown extensions along the venous system toward the heart. Wilm's tumor (nephroblastoma) and, less frequently, rhabdosarcoma can present like this. Although these are not technically "cardiac tumors," they may require cardiopulmonary bypass for excision. The prognosis of secondary malignant cardiac tumors is usually poor and based on the progression of, and response to treatment of, the primary malignancy.

As can be seen from Figure 31.28, the prevalence of different tumors varies with age from fetus through to adolescence [108].

The most common cardiac tumor in children is rhabdomyoma, comprising more than half the cardiac tumors in most pediatric series [109] (Table 31.10). Rhabdomyoma is usually (although not exclusively) associated with tuberous sclerosis complex. This autosomal dominant condition with variable penetrance is mostly related to abnormalities in either of two genes, TSC1 and TSC2, which are tumor suppressor genes. About two-thirds of cases of tuberous sclerosis complex arise as de novo mutations, and about 80% of cases have an identifiable abnormality in TSC1 or TSC2.

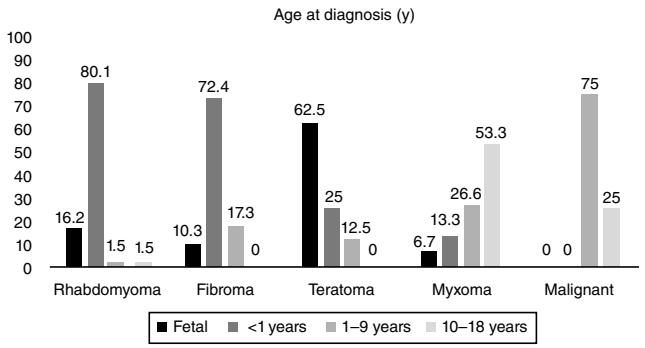


Figure 31.28 Prevalence of benign and malignant tumors according to different age groups. (Source: Tzani et al. [108]. Reproduced with permission of SAGE Publications.)

Table 31.10 Frequency distribution of cardiac tumors in children

Primary benign	***Frequency (%)***
Rhabdomyoma	40–60
Teratoma	15–19
Fibroma	12–16
Myxoma	2–4
Haemangioma	5
Lymphangioma	}
Haemangiopericytoma	} Very rare
Oncocytic tumors	}
Primary malignant	
Rabdomyosarcomas	2
Fibrosarcomas	2
Secondary metastatic tumors	
Neuroblastoma	}
Leukaemia	} Very
Lymphoma	} rare
Melanoma	}

Source: Uzan et al. [109] / Springer Nature / CC BY 2.0

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Tuberous sclerosis complex affects many tissues in the body with lesions in the brain usually having the most profound clinical effects, while kidney, liver, heart, and lung lesions can also be clinically significant. Cardiac rhabdomyomas appear in the second half of pregnancy and tend to regress after birth. As many as 90% of patients with tuberous sclerosis complex have cardiac tumors at birth, but the figure decreases to about 20% in adults. There may be multiple cardiac rhabdomyomas in patients with tuberous sclerosis complex, usually occurring in the ventricular muscle or on the atrioventricular valves.

The drugs Everolimus and Sirolimus, inhibitors of the mammalian target of rapamycin (mTOR), have been shown to be effective in controlling seizures in patients with tuberous sclerosis complex, as well as reducing the size of subependymal giant cell tumors in the brain and rhabdomyomas in the heart. The mTOR is involved in the control of the cell proliferation cycle which is accelerated abnormally by defective TSC1 or TSC2 genes. In a recent systematic review of patients with TSC and cardiac rhabdomyomas, 90% of patients experienced a reduction in the size of symptomatic tumors when treated with either everolimus or sirolimus, thus offering a possible alternative to surgical resection for these patients [110].

Fibromas are the tumors of fibroblast cells and are the second most common cardiac tumor in children, accounting for 10–25% in most series. There is an association with the presence of nevoid basal cell carcinoma syndrome (also known as Gorlin syndrome) and cardiac fibromas. They are slow-growing or stable in size and most commonly occur in the ventricular free wall or interventricular septum. Unlike rhabdomyomas, they do not usually recede. However, the patient often grows faster than the tumor so adverse effects can become less severe with time. Partial resection of the tumor is acceptable for symptom relief and cardiac transplantation or single ventricle palliation has been used with some success for cases deemed non-resectable [111]. The overall prognosis is better in tumors that are able to be successfully resected.

Myxomas occur rarely in children, making up less than 10% of most series, and are largely seen in older children. They are very rare in the fetus or neonate. However, they are the commonest cardiac tumors in adults with females affected slightly more than males. The left atrium is the most common site for these tumors (75%), mostly arising from the fossa ovalis, but they can arise from any of the cardiac chambers. They are often pedunculated and lobular, may have frond-like projections but can also be sessile. About 10% of myxomas are associated with the Carney complex, an inherited tumor disorder characterized by cardiac and extra-cardiac myxomas, schwannomas, and endocrine tumors. Cardiac myxomas do not recede and need to be surgically resected in order to minimize complications due to cardiac obstruction or embolization as discussed later in this section.

Teratomas account for a small but varying proportion of cardiac tumors, 2% in one series [112], although in neonates they are second commonest after rhabdomyoma [109]. They are comprised of cells from one or more of the embryonic germ lines and are midline tumors that usually present early in life and are increasingly being diagnosed on fetal ultrasound. They can grow rapidly and if not diagnosed on fetal ultrasound, they will very likely present early in the neonatal period. It is very unusual for a teratoma to be an incidental finding.

The majority of teratomas are not malignant and surgical resection is the usual treatment. Although often arising above the heart in the anterior mediastinum, the heart and great vessels may be involved in these sometimes very large masses. They can occur within the pericardium, often causing pericardial effusion and/or compression of the right atrium. They derive blood supply from fibrous attachment to the aorta or pulmonary trunk which may make resection difficult, with some procedures requiring cardiopulmonary bypass. *In utero* and *ex utero*, fetal surgery has been successfully performed for mediastinal teratoma.

Hemangiomas can occur anywhere in the heart and may be asymptomatic, may regress, and may respond to medical therapy. Depending on the position and complications, some will require surgical resection. Some can present in infancy. There have been major advances in understanding the biology of various forms of hemangioma, and prognosis and treatment are evolving. If surgery is not required urgently, cardiac hemangiomas should be assessed by an expert vascular malformation clinic, as medical therapy may be available and detailed prognostic information may be attainable, particularly with regard to the possibility of spontaneous regression.

Pathophysiology of cardiac tumors

The pathophysiology of the various cardiac tumors is dependent upon their location as well as their size and relationship to surrounding structures.

Tumors may protrude into the cardiac chambers or outflow tracts causing obstruction to flow. In the case of rhabdomyomas, many of these tumors will recede with time so an expectant, conservative management strategy may be indicated. However, severe obstruction will require surgical resection or de-bulking (Figures 31.29 and 31.30). Rhabdomyomas can cause hydrops or fetal demise by mechanisms such as arrhythmia, obstruction to flow or extrinsic compression of coronary arteries causing loss of functional myocardium. The neonatal or infantile presentation may be due to similar mechanisms with arrhythmia being present in about 30% of cases in one series [112].

Fibromas can present with a variety of symptoms or signs depending upon their location and size (Figure 31.31). Arrhythmia is again a feature, with ventricular tachycardia (VT) being particularly common, 64% in one series [112], which resolved after resection or debulking in 13 of 16 patients. Post-surgical complications tend to be related to the location of the tumor with resultant regional wall motion abnormalities at the site of resection or valvular pathology requiring reoperation in some cases. Heart transplantation is considered in cases of massive tumors that are thought not to be resectable.

Myxomas are often readily distinguished from other cardiac tumors due to the fact that they arise most commonly from the left side of the fossa ovalis and have a characteristic pedunculated appearance. They are seen to intermittently obstruct the mitral inflow to the left ventricle in a

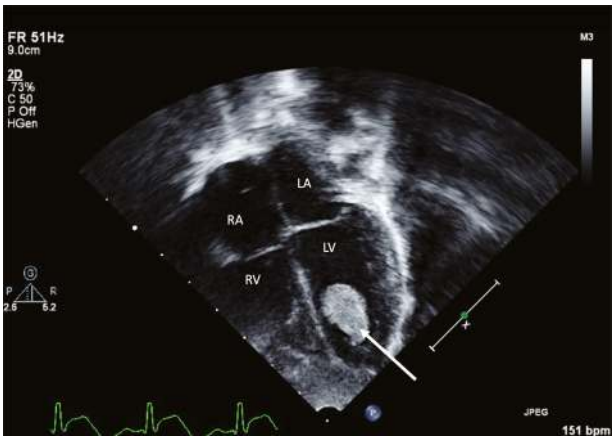


Figure 31.29 Transthoracic echocardiography image of rhabdomyoma in the left ventricle (arrow) of a 3-month-old infant, diagnosed antenatally and followed with serial scans. This tumor did not need resection. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. Courtesy of Dr. Bryn Jones, Cardiologist, The Royal Children's Hospital, Melbourne, Australia.

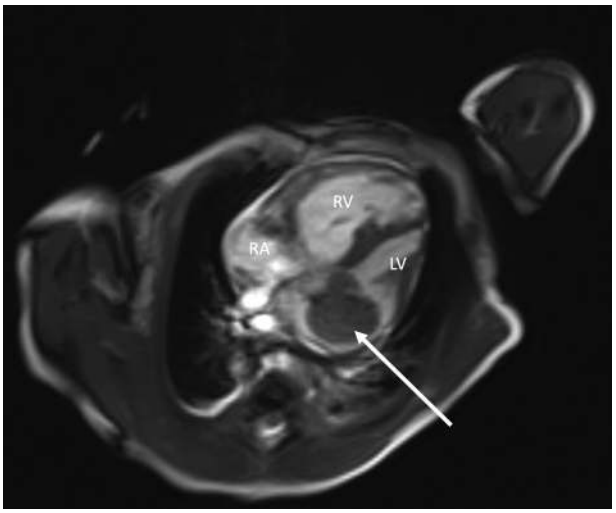


Figure 31.30 MRI image of rhabdomyoma (arrow) arising from the mitral apparatus and obstructing left ventricular inflow in a neonate. This was diagnosed antenatally and required resection in the neonatal period due to obstruction to mitral inflow. RA, right atrium; RV, right ventricle; LV, left ventricle. Courtesy of Dr. Bryn Jones, Cardiologist, The Royal Children's Hospital, Melbourne, Australia.

"ball-valve" type manner. Not only can they present with symptoms of obstruction to cardiac output, which can be intermittent and positional, but they are also often implicated in embolic phenomena. The emboli consist of a thrombus formed on the tumor surface or fragments of the tumor itself. In fact, cardiac myxomas can be found in the brain after having embolised and seeded the cerebral vasculature. The embolic phenomena can lead to presentation similar to infective endocarditis with any tissue bed in the arterial tree potentially affected. Non-specific symptoms and signs including fever and malaise occur in about a third of patients. These constitutional symptoms are thought due to increased levels of the inflammatory mediator interleukin-6.

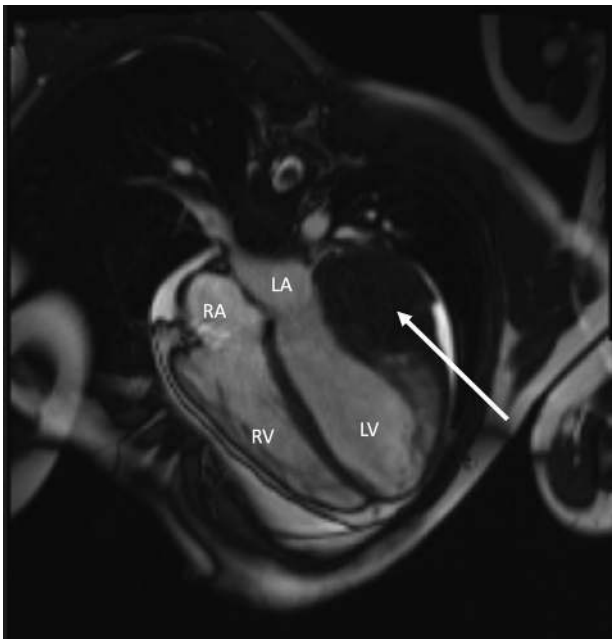


Figure 31.31 Magnetic resonance image of a large fibroma of the base of the LV in an adolescent. This was under surveillance with serial scans and eventually required resection due to the development of ventricular tachycardia. Courtesy of Dr. Bryn Jones, Cardiologist, The Royal Children's Hospital, Melbourne, Australia.

Surgical approaches and outcomes for cardiac tumors

Surgical planning and decision-making for cardiac tumors will depend on the following factors: tumor type, tumor position, pathophysiologic effects, and the risks of excision. Most procedures for cardiac tumors will involve CPB, but occasional lesions involving structures that do not require opening of the heart may not. Sternotomy is the usual approach, but various less invasive approaches have been used for tumors such as atrial myxoma where the lesion is pedunculated, and the surgery can be performed through a left thoracotomy or partial sternotomy.

For pedunculated intravascular tumors that have grown into the heart along the great veins, e.g., Wilms tumor, strategies to deal with the intravascular tumor, prevent embolization, and have adequate CPB may require tailoring of the perfusion plan to the exact anatomy and include having venous drainage from sites external to the heart (Figure 31.32).

If cardiac tumors can be removed without disrupting the postoperative function of the heart, outcomes are usually good. The degree of resection attempted will be informed by this, as partial resection may be preferable for rhabdomyomas and fibromas if more radical surgery will jeopardize the functional outcome. As these tumors are slow growing or tend to stabilize and even regress, partial resection that relieves symptoms will often be adequate. Atrial myxomas are occasionally locally aggressive and may recur if the base is not adequately excised. The outcome for surgical excision of myxomas is usually very good, but occasionally, a child with myxoma is in the high-risk familial, genetic group, making recurrence more likely both locally and at a separate cardiac location.

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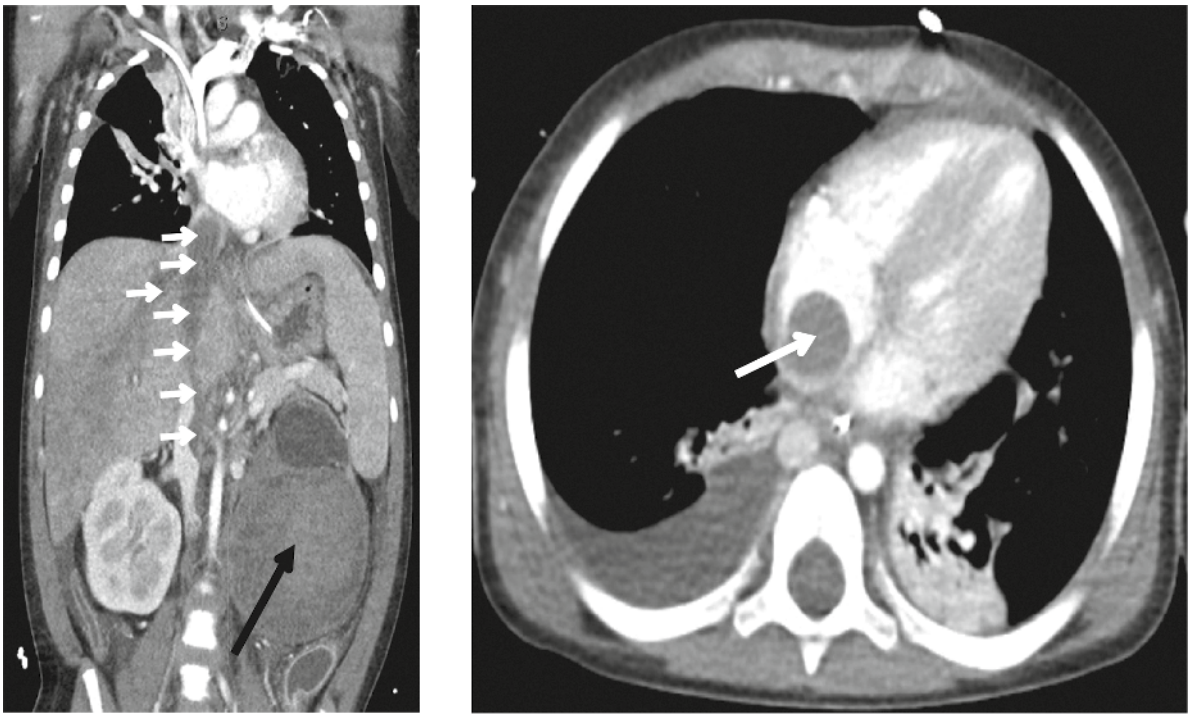


Figure 31.32 A 4-year-old child with Wilm's tumor extension into the right atrium. (A) Computed tomography scan with contrast of abdomen and thorax, coronal view. There is a large 7 × 8 cm left renal mass (black arrow) with extensive tumor thrombus involving the left renal vein, inferior vena cava, right hepatic vein, and right atrium (white arrows). (B) Axial view demonstrating large tumor thrombus in the right atrium. (Arrow). The patient underwent radical left nephrectomy with tumor thrombus removal and closure of the patent foramen ovale with cardiopulmonary bypass.

Teratomas arising at the base of the heart may be large and grossly distorted and may involve the great vessels and the coronary arteries. Surgery may be technically difficult and a multidisciplinary team involving cardiology, medical imaging, cardiac surgery, oncology, perfusion, and anesthesia should carefully plan the approach to excision. Successful excision, however, should be curative.

Anesthesia considerations for cardiac tumors

Anesthesia for the wide range of possible procedures relating to cardiac tumors needs to be tailored to the patient's condition and the planned surgical approach. Most rhabdomyomas will not require surgery, but those that do will usually have a significant cardiovascular impairment which will need to be defined. Patients with tuberous sclerosis complex are likely to have multiple other systems involved and behavioral issues such as developmental delay and autism that will require special attention to minimize distress for the patient and family.

Tumors that involve the right side of the heart and pedunculated lesions that have passed centrally from peripheral origins may require consideration with regard to where vascular access is placed, with lesions involving the inferior vena cava (such as the venous extension to the atrium of Wilms' tumor) having vascular access in the upper limb and avoiding femoral central access. Similarly, lesions arising in the neck and upper limbs (which are less common but can occur with rhabdosarcoma) require lower limb vascular access to avoid the possibility of injected medications and fluids being obstructed from reaching the central circulation during resection.

Patients with malignant lesions involving the heart will often have received chemotherapy. Complications of these therapies should be assessed. Bone marrow status should be checked to confirm or plan for appropriate recovery or management of anemia, thrombocytopenia, and neutropenia. Consideration should be given to previous use of agents that sensitize the lungs to hyperoxia, such as bleomycin, or those with potential for cardiotoxicities, such as doxorubicin or other agents of the anthracycline class. Surgery is rarely indicated for malignant lesions not arising in the heart, but debulking recurrent lymphoma that has invaded the pericardium from the anterior mediastinum is occasionally required. These recurrent lesions involving the pericardium are rarely of size or in a position to create the issues described in the section on mediastinal masses. Lymphomatous pericardial effusion may also need drainage either for diagnostic purposes or to relieve tamponade. Careful assessment and management of the patient with the potential for tamponade are required (see previous section).

Teratomas arising in the midline at the base of the heart will usually be present at birth and may be very challenging for all clinicians involved. The patient's preoperative condition may be poor, with obstruction to major vessels, distortion of the heart and coronary vessels, and potentially high-output cardiac failure and persistent pulmonary hypertension due to the large blood supply of the lesion. Excision without injuring important cardiac structures (such as

coronary arteries), leading to postoperative myocardial dysfunction, may be difficult and intraoperative blood loss may be extensive and difficult to control. Pre-operative planning to support massive transfusion and prevention of coagulopathy is appropriate.

Anesthesia may be required for interventional imaging procedures to define, biopsy or treat tumors of the heart.

KEY POINTS: ANESTHESIA FOR CARDIAC TUMORS

- The most common cardiac tumor in childhood is rhabdomyoma.
- Myxomas are the commonest intracardiac tumors in adults, but they are rare in young children.
- Teratomas are midline and may arise at the base of the heart and present as large tumors in the neonatal period.
- Malignant tumors involving the heart are rare and have a poor prognosis.
- CBP may be required for pedunculated tumors that have grown along venous paths to the atrium, such as a Wilms tumor.
- Anesthesia for cardiac tumors is based on the preoperative patient condition and the nature of the surgery planned.

Aortic aneurysm and aortopathy in children

Classification and definition of aortic aneurysms (and aortopathy)

An aortic aneurysm is defined as a permanent localized dilatation of the aorta, having at least 50% greater diameter than that expected for age and sex [113]. It may occur anywhere from the aortic valve annulus to the bifurcation of the abdominal aorta. A true aneurysm involves all layers of the vessel wall (intima, media, and adventitia). Those involving circumferential dilatation of the vessel are called fusiform aneurysms and are the most commonly occurring type. Saccular aneurysms are berry-like expansions, sometimes with a narrow neck, at a weak spot in the vessel wall. Aneurysms of a single sinus of Valsalva are of the saccular type.

False aneurysms, also known as pseudoaneurysms, can occur secondary to local pathologies, such as trauma or infection, and involve the creation of a space in continuity with the lumen of the vessel. A false aneurysm is not bounded by the vessel wall but by external tissue, such as the wall of an abscess that has eroded the vessel or the site of previous trauma where hematoma and fibrosis now form the containing layer.

A mycotic aneurysm is a specific term that relates to the formation of infection within the wall of an artery secondary to embolization from infective endocarditis seeding the vasa vasorum of the arterial wall.

Dissecting aneurysms (or "dissections") occur when an aneurysm, usually fusiform, creates an intimal tear, sparing the adventitia and sometimes the media. The arterial pulsations then split the internal layers, creating a blood-filled space in the wall, which tracks along the vessel and continues to split the layers apart, still leaving the adventitia intact. The dissection may rupture internally by tearing the intima at another site or eventually rupture through the adventitia externally. The dissection process can occlude branches of the vessel, leading to end-organ ischemia, and may be the site of thrombosis and/or a source of emboli.

The term "aortopathy" refers to the clinical association of aortic pathophysiological abnormalities and aortic dilatation [114]. Aortopathy is increasingly being recognized as part of the spectrum of presentations and natural history of many types of congenital heart disease (CHD).

Incidence, anatomy, and natural history of aortic aneurysms in children

Aortic aneurysms are rare in children and can be classified according to the site, type, acuity, and underlying pathology. Dissection of the aorta is extremely rare in children and, if it occurs, it tends to occur later in childhood in patients with underlying connective tissue disorders and large fusiform aneurysms.

The majority of pediatric aortic aneurysms involve the ascending aorta and the aortic root with far fewer occurring in the transverse arch, descending thoracic aorta, or abdominal aorta. The commonest causes of aneurysms of the ascending aorta and aortic root in children are genetic conditions, especially connective tissue disorders, with Marfan syndrome being the most common of these. Inflammatory conditions such as autoimmune disease and arteritis may also affect the aorta and be associated with aneurysm formation. Inflammatory conditions such as Takayasu arteritis or Kawasaki disease will usually have multifocal arterial lesions, often stenotic, as well as other features, such as systemic illness, with aortic aneurysm as an occasional complication. As alluded to above, there is an increasing number of patients with congenital heart disease surviving into adulthood and displaying signs of aortopathy not previously seen.

Genetic conditions associated with aortic aneurysm

Marfan syndrome

Marfan syndrome is the genetic condition most commonly associated with an aneurysm of the aorta, usually involving the ascending aorta and often the aortic root. The clinical diagnosis of Marfan syndrome is based on the revised "Ghent" criteria [115, 116] (Tables 31.11 and 31.12). Variations based on the presence of family history and the age of the patient are included. The existence of related syndromes, including those featuring aortic dilatation but differing genetics and a spectrum of either differing or overlapping (with Marfan) associated features, such as Sphrintzen–Goldberg syndrome, Loeys–Dietz syndrome, and the vascular form of Ehlers–Danlos syndrome, are specifically included in the differential diagnosis and actively sought, to make misdiagnosis less likely. "Typical" patients with Marfan syndrome will often have particular facial features and body habitus with long thin limbs, tall stature, and hypermobility of joints. Arachnodactyly

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Table 31.11 Revised Ghent criteria

In the absence of family history	In the presence of family history
Aortic root dilation (*z*-score at least 2 or aortic root dissection) and ectopia lentis	Ectopia lentis and Family history of Marfan syndrome as defined by new criteria
Aortic diameter (*z* at least 2 or aortic root dissection) and a pathogenic FBN1 variant as defined above	Systemic score at least 7 points[a] and Family history of Marfan syndrome as defined by new criteria
Aortic criterion (aortic diameter *z* at least 2 or aortic root dissection) and a systemic score at least *7* (see Table 31.12)	Aortic criterion (aortic diameter $z \geq 2$ above 20 years old, $z \geq 3$ below 20 years, or aortic root dissection)[a] AND Family history of Marfan syndrome as defined by new criteria
Ectopia lentis and a pathogenic FBN1 variant	

[a] The diagnosis of MFS is made in the absence of discriminating features of other syndromic disorders, such as Loeys-Dietz syndrome or vascular Ehlers–Danlos syndrome.

Source: Rigelsky & Moran [116]. Reproduced with permission of Wolters Kluwer Health, Inc.

Table 31.12 Marfan systemic score

Finding	Score
Wrist and thumb sign	3
Wrist or thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Plain pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Reduced US/LS and increased arm/height and no severe scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Facial features – (3/5) dolichocephaly, enophthalmos, down slanting palpebral fissures, malar hypoplasia, retrognathia	1
Skin striae	1
Myopia less than –3 diopters	1
Mitral valve prolapse	1

Source: Rigelsky & Moran [116]. Reproduced with permission of Wolters Kluwer Health, Inc.

can be demonstrated by the thumb sign (the adducted thumb has the whole of the nail protrude beyond the ulnar margin of the palm) and the wrist sign (when encircling the opposite wrist, the thumb, and fifth finger overlap). These and many other physical signs are codified in the Ghent criteria.

Marfan syndrome has an incidence of between 1 in 3,000 and 1 in 10,000 with the variation likely due to missed diagnoses in some populations. [117] It is an autosomal dominant condition with variable penetrance although about 25% of cases involve new mutations, with some effect

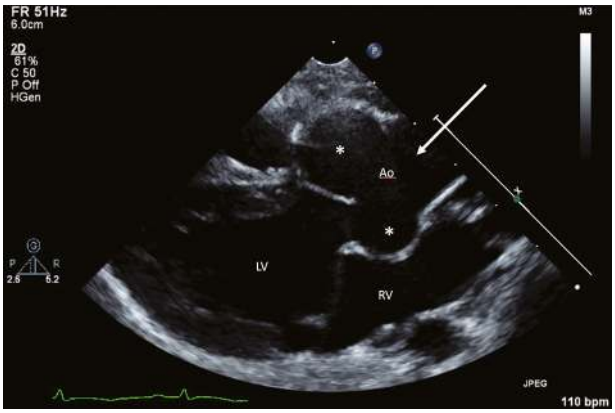


Figure 31.33 Parasternal long axis echo view of the dilated aortic root in a patient with Marfan syndrome. Arrow denotes the dilated root, asterisks the dilated sinuses of Valsalva. Ao, aorta; LV, left ventricle; RV, right ventricle. Courtesy of Dr. Bryn Jones, Cardiologist, The Royal Children's Hospital, Melbourne, Australia.

of parental age. Mitral valve regurgitation may also occur, often earlier than the aortic dilatation but usually with less severe consequences. Aortic regurgitation is secondary to aortic root dilatation (Figure 31.33). Skeletal abnormalities including long bone overgrowth and ophthalmic abnormalities including ectopia lentis (lens dislocation) are the other main features of the syndrome. The abnormal gene in most patients with Marfan syndrome is FBN1, which lies on chromosome 15 and encodes for type 1 fibrillin, a protein that forms part of the microfibrils in the extracellular matrix, contributing to the formation and maintenance of elastic fibers. There are a large number of mutations of FBN1 that cause Marfan's syndrome, most of them altering a single amino acid. The phenotype produced is highly variable and does not correlate well with the different mutations. There are also a series of related "fibrillinopathies" with associated genetic abnormalities that give rise to variants of Marfan syndrome; these may not have all the clinical features of Marfan syndrome but some are associated with aortic aneurysm. There is a rare neonatal form of Marfan syndrome which is usually rapidly progressive and fatal. About 10% of patients with Marfan phenotype have a mutation in TGF-βR2, which encodes for transforming growth factor beta-receptor type II, a controller of extracellular matrix production, interacting with fibrillin formation, and some authors argue that these patients should be classified as having Loeys–Dietz syndrome as this diagnosis highlights the risk of more severe aortic dilatation and dissection (see later in this section).

Management usually includes pharmacological treatment aiming to prevent or slow the progression of aortic root dilation, such as beta-blockade, which is probably effective [118]. The evidence for beta-blockers in children with Marfan syndrome is even less robust, although most centers still routinely use this therapy as the first line. Angiotensin II receptor blockers (ARBs) such as losartan, may be used if beta-blockers are not tolerated with studies showing equal efficacy. In patients with Marfan syndrome and aortic dilatation, ARBs are added to beta-blockers although the evidence for this is mixed. Advice should be given about avoiding

activities that might cause aneurysm rupture, such as contact sport or isometric efforts involving a Valsalva maneuver, such as weight-lifting, whereas mild to moderate aerobic activity is acceptable and in fact, encouraged. Pregnancy increases the risk of aortic rupture, especially if the aortic root is already 4 cm at the beginning of the pregnancy. Regular ophthalmic follow-up is also required for patients with Marfan syndrome. Historically, 50% of patients with Marfan syndrome died before the age of 40, whereas more recently median survival can be greater than 70 years [119].

Serial echocardiography to monitor the aortic root and also the aortic and mitral valves and the pulmonary artery should commence at diagnosis of Marfan syndrome and be at least yearly at first. Significant aortic dilatation is unusual in children less than 10 years of age. Following the "*z* score" (z score of +2 is 2 standard deviations above mean normal diameter for age or body surface area, for example) for aortic root dimensions is appropriate in childhood, rather than an absolute value for aortic dimension. Correlation of the aortic diameter with the body surface area can also be used to track dilatation with respect to overall patient size. Indications for elective surgery for aortic root dilatation in older children will depend on both the degree of the dilatation and the rate of increase in size. Dissection of the aorta due to Marfan syndrome is very rare in childhood. Associated aortic or mitral valve regurgitation is a more common indication for surgery in children.

Loeys-Dietz syndrome

Loeys-Dietz syndrome (LDS), first described in 2005, is an autosomal dominant inherited condition characterized by vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections), skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus, cervical spine malformation and/or instability), craniofacial features (widely spaced eyes, strabismus, bifid uvula/cleft palate, and craniosynostosis that can involve any sutures), and cutaneous findings (velvety and translucent skin, easy bruising, and dystrophic scars). Individuals with LDS are predisposed to widespread and aggressive arterial aneurysms and pregnancy-related complications including uterine rupture and death [120].

Diagnosis is by the presence of one of the associated genes (SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, or TGFBR2) along with characteristic features in the proband or family members.

The arterial disease is more aggressive than that in other connective tissue diseases such as Marfan syndrome, with aortic dissection and rupture occurring at younger ages and smaller aortic diameters, occasionally described in children as young as 3 months of age [121]. One Center's experience with elective aortic root replacement in patients with LDS showed 95% survival and 54% freedom from reoperation at 10 years. The average age at operation was 10 years, the average aortic z-score was 7.8 and most had a valve-sparing root replacement [121].

Ehlers–Danlos syndrome

Ehlers–Danlos syndrome has six subtypes. The main general features are hyperextensible skin, hypermobile joints, and connective tissue fragility. Type IV is known as the vascular type. This is an autosomal dominant condition associated with mutations in the COL3A1 gene on chromosome 2, which encodes for the collagen alpha 1 (III) chain. It has an incidence of about 1 in 5,000–20,000. About 50% of cases arise as new mutations. This variant is associated with arterial aneurysms at many locations, including the aorta. There is also an association with gastrointestinal perforation and uterine rupture in pregnancy related to vascular Ehlers–Danlos syndrome. Recognition of the syndrome before these life-threatening complications occur may allow prevention or earlier intervention.

Other examples of syndromic genetic conditions associated with aortic aneurysm formation include Noonan syndrome, Williams syndrome, autosomal dominant polycystic kidney disease, Turner syndrome, homocystinuria, osteogenesis imperfecta, and pseudoxanthoma elasticum.

Sinus of Valsalva aneurysms

Aneurysm of a sinus of Valsalva may affect any one of the three sinuses. Dilatation involving all three sinuses is classified as an aneurysm of the root of the aorta and usually relates to fusiform dilatation due to connective tissue disease [122]. The sinuses of Valsalva together form the aortic root, originating at the aortic annulus and terminating at the sinotubular junction, where the ascending aorta begins. Although acquired aneurysms of the sinus of Valsalva can occur due to trauma, infection, or surgery, most are congenital. Aneurysm of the right sinus of Valsalva is the commonest, accounting for 60–85%, with aneurysms of the non-coronary sinus accounting for most of the rest and aneurysm of the left sinus accounting for less than 5%. There is an association between VSDs just below the annulus fibrosus, and aneurysm of the sinus of Valsalva, where there is a separation of the aortic media from the annulus fibrosus and abnormal elastin deposition, creating a weak area that expands to create the aneurysm. An aneurysm of the right sinus of Valsalva can rupture into the pulmonary artery or any chamber of the heart except the left atrium. This creates a fistula that may be sufficiently high-flow to cause acute cardiac failure. Rupture into the pericardium will cause tamponade. The left and non-coronary sinuses of Valsalva can rupture into any cardiac chamber or the pericardium, but not the pulmonary artery when the great arteries are normally placed. The commonest fistulas are from the right sinus of the Valsalva aneurysm to the right ventricle (about two-thirds). Unruptured aneurysms may be large and obstruct right ventricular outflow or cause coronary compression. Congenital aneurysms of the sinus of Valsalva are more common in males (4: 1) and in some Asian communities, where there is a stronger association with supracristal (doubly committed) VSDs. There is also an association with aortic regurgitation and bicuspid aortic valve.

Aortopathy and aortic dilation with CHD

Bicuspid aortic valve (BAV) is the most commonly occurring CHD with a prevalence of 1–2% in the general population. Concomitant aortic dilatation is seen in up to 80% of patients (Figure 31.34). The lifetime risk of aortic dissection in patients with BAV is reported as up to 9 times that of the general population [123]; however, the large denominator of people

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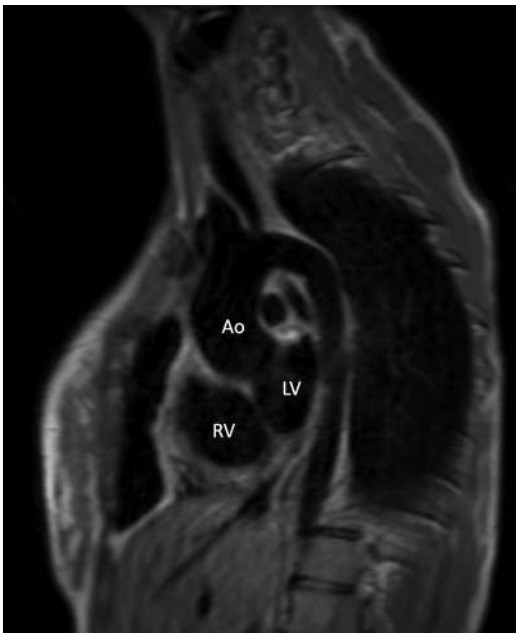


Figure 31.34 Dark blood MRI image of the dilated ascending aorta in a patient with the bicuspid aortic valve. LV, left ventricle; RV, right ventricle; Ao, aorta. Courtesy of Dr. Bryn Jones, Cardiologist, The Royal Children's Hospital, Melbourne, Australia.

with asymptomatic BAV and no aortic dilatation, discovered incidentally with routine cardiac screening, has led to a general reduction in the estimate of dissection risk [124]. Familial studies suggest an autosomal dominant inheritance pattern with incomplete penetrance. There is a 9–20% chance of identifying BAV in first-degree relatives of an affected proband, thus the guidelines recommend echocardiographic screening in all first-degree relatives. There are a small number of genes so far identified in connection with familial non-syndromic BAV aortopathy, including NOTCH-1, SMAD6, and MAT2A. BAV is present in 40% of patients with Turner syndrome and is associated with the presence of mutations in the Tissue Inhibitor of Matrix Metalloproteinase 1 and 3 (TIMP 1 and TIMP 3) genes.

Coarctation of the aorta accounts for 5–8% of all CHDs with more than half of these cases being associated with other lesions such as BAV or mitral valve pathology. Genetic influences play a role and there is a slight male predominance. Further, 10% of patients with Turner syndrome also have coarctation. A dilated ascending aorta and an aortic arch are commonly found in patients presenting late with previously asymptomatic coarctation. This is in contrast to those presenting in the neonatal period, especially if in association with a VSD, whereby blood is preferentially directed into the pulmonary trunk and across the ductus arteriosus. It seems that early operation for coarctation is protective against future aortic dilatation.

Conotruncal defects including truncus arteriosus, transposition of the great arteries (TGA), tetralogy of Fallot (TOF), and double outlet right ventricle are frequently associated with thoracic aortic dilatation [124]. However, there does not seem to be the same risk for progressing to aortic dissection with conotruncal lesions as there is with aortopathy associated with BAV. TOF is the commonest form of cyanotic CHD and accounts for 10% of all CHD. Dilatation of the aortic root and ascending aorta is common in ToF and can be observed in fetal echocardiography. Persistent aortic root dilatation is more commonly reported in adult patients after childhood TOF repair, now that survival to adulthood from this condition is around 90%. A right-sided aortic arch, male gender, history of an aortopulmonary shunt, and complete repair at an older age have been associated with late aortic dilatation [123]. Significant regression of indexed aortic root diameters over time after early repair in infancy, with a chance of normalizing the initially dilated root within 7–8 years has been demonstrated. [123]

Secondary aortic root dilatation can be seen after surgical correction of congenital heart diseases during which the native aortic root is replaced with a pulmonary homograft (Ross procedure), is modified (the arterial switch operation [ASO] as described by Jatene), or reconstructed (Damus Kaye Stanzel anastomosis for single ventricle palliation of hypoplastic left heart lesions). Literature on this particular variant of aortopathy is less extensive than that for BAV or TOF as it was only recognized as an emerging feature of the disease within the last decade or so. Risk factors for late neoaortic root dilatation and regurgitation after ASO are the presence of a VSD, previous pulmonary artery banding, older age at repair, and the association with coarctation. Technical factors such as acute angulation of the aortic arch after ASO and closure of the VSD through the pulmonary artery, have been associated with late aortic regurgitation and aortic dilatation in some reports [123]. In a study with a median follow-up of 9 years after Fontan completion, neoaortic root progressively dilated out of proportion to body size over time, with 98% of patients having a root z-score of >2 at the most recent follow-up [125].

Pathophysiology of aortic aneurysms

The law of Laplace (wall tension is proportional to transmural pressure multiplied by vessel radius), as modified and applied to blood vessels, helps explain why aneurysms tend to expand and rupture. The wall tension is proportional to the pressure differential across the wall and the radius of the vessel. From these relations, it can be seen that, as a vessel dilates, its radius increases and, even with the internal pressure unchanged, the wall tension will increase, making further dilatation and rupture more likely. Alternatively, an increase in pressure inside the vessel relative to the outside will also increase wall tension making dilatation and rupture, again, more likely. Tissue stress can be decreased by an increase in the thickness of the wall (allowing the "retaining force" to be distributed over more tissue). However, the dilatation process is often associated with thinning of the vessel wall, which increases the stress on the tissue, thereby increasing the likelihood of expansion of the aneurysm. Some pathologies may be associated with changes, such as fibrosis, that thicken the wall and change the tissue characteristics, decreasing tissue stress and potentially stabilizing an aneurysm. Aneurysmal expansion and, eventually, more rapid dilatation and rupture are likely outcomes, but the time frames for these processes are notably variable depending on the causative pathology. Dissection of the inner layers may occur as the tissues distend or the underlying pathology progresses. In most conditions

associated with aortic aneurysm, abnormalities of the aortic media develop so that loss of elastin and changes in collagen are progressive, with cystic degeneration and necrosis of portions of the media a common finding. If the intima splits with dilation or other pathology, the abnormal media will be especially prone to dissection.

The same picture of maladaptive remodeling of the aortic media seen in Marfan syndrome is also noted in patients with BAV and conotruncal defects. There is extracellular matrix degradation associated with noninflammatory loss of vascular smooth muscle cells. The vascular smooth muscle cell apoptosis is thought to occur secondary to excessive activity of a group of degradative enzymes known as matrix metalloproteinases (MMPs) [124]. Despite similarities in pathophysiology, the frequency of aortic dilation, and more importantly, the risk of aortic dissection, differ considerably among the aortopathies of Marfan syndrome, BAV, and conotruncal defects, as noted in the previous section. In light of these differences, the criteria for surgical intervention also differ.

The exact mechanism of aortic wall degradation is unclear and is thought to be due to a combination of hemodynamic shear stress from altered or abnormal flow in the proximal aorta (the hemodynamic theory) and genetic influences on the elastic fibers and vascular smooth muscle cells in the extracellular matrix (the genetic theory).

Surgical approaches for aortic aneurysms in children

Historically, aortic root replacement consisted of the Bentall procedure, which involved mechanical aortic valve replacement, a tube replacement of the aortic root and reimplantation of the coronary arteries. This procedure had very good results and is still widely used in adults. In children, the issues of lifelong anticoagulation associated with prosthetic aortic valves, and the failure of growth and long-term complications of prosthetic valves and conduits were a major stimulus for attempting surgery to replace the aortic root while leaving the native aortic valve intact. The major surgical advance in aortic root replacement over the last few decades, especially for children, has been the evolution of valve-sparing aortic root replacement [126]. Two major techniques were introduced and there have been many variants. Remodeling, introduced by Yacoub, involved a proximally scalloped aortic tube graft, which is sutured above the aortic annulus with the longer scalloped portions sewn along the line of the attachments of the aortic valves, mimicking the sinuses of Valsalva and providing some distensibility of the aortic root, which is closer to the normal physiology. This is technically a more straightforward procedure than the alternative reimplantation techniques but still requires coronary re-implantation. The greatest medium-term risk with the remodeling technique was recurrent aortic annulus dilatation and aortic regurgitation, especially in children who usually have an underlying connective tissue disorder. Various modifications to support the aortic annulus and prevent subsequent dilatation and aortic regurgitation have been added to this technique to decrease that risk.

Reimplantation, introduced by David, anchored the aortic tube to the ventricular side of the aortic annulus with a second proximal suture line in a position similar to that used for the remodeling technique. The major difference in the medium term is that the aortic annulus is supported and recurrent dilatation at that level and consequent aortic regurgitation should be prevented [127]. In fact, early results showed problems with interference with aortic valve function, partly due to the decrease in aortic annulus diameter, which meant that aortic valve prolapse and poor coaptation could occur, leading to aortic regurgitation. Subsequent techniques have incorporated aortic valve surgery to tailor the valve leaflets to the new geometry and decrease the risk of regurgitation. The reimplantation technique, as originally described, has evolved with more recent techniques and preformed devices focused on restoring the convex curve of the aortic root, which should better mimic the normal function of the sinuses of Valsalva in relation to aortic valve function and coronary artery flow. Ascending aortic dilatation can continue to occur after the aortic root has been replaced (Figure 31.35).

Modern myocardial preservation that affords low morbidity from the long cross-clamp times required for this, often extensive, reconstructive surgery of the aortic root, aortic valve, and coronary reimplantation, have facilitated the advances in this area. The presence of aortic regurgitation preoperatively, common in patients with a dilated aortic root, requires isolated coronary perfusion or retrograde coronary perfusion to effectively deliver cardioplegia.

A recent, exciting development in the prevention of dissection in patients with aneurysms of the aortic root or ascending aorta has been personalised external aortic root

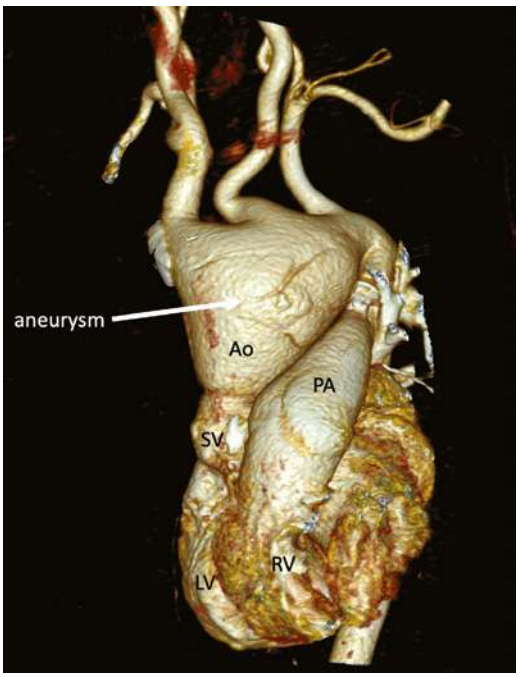


Figure 31.35 Reconstructed computed tomography angiogram of ascending aortic aneurysm after aortic root replacement. Ao, aorta; SV, sinus of Valsalva; LV, left ventricle; RV, right ventricle; PA, pulmonary artery. Courtesy of Dr. Bryn Jones, Cardiologist, The Royal Children's Hospital, Melbourne, Australia.

support (PEARS). This is a technique whereby a 3D mesh model of the patient's aortic root and the ascending aorta is custom made by computer-aided design and is then implanted via sternotomy but usually not requiring CPB (73% off the bypass in this study), around the existing aortic root and ascending aorta. The mesh provides a "structural framework" against which the aorta is prevented from dilating. This group has published a series of cases from 2004 to 2017 in which 117 patients received an external mesh implant, initially at one center, and then expanding to include 14 teams [128]. The purpose of the procedure is to prevent aortic dissection, so inclusion criteria were aortic diameters of 40–50 mm in asymptomatic patients over the age of 16 years. Results are encouraging so far although the authors acknowledge that long-term follow-up has not yet occurred. They also plan to publish shortly on a series where PEARS has been used to support the neo-aorta after the Ross procedure and they speculate on future potential uses in situations such as aortic dilatation in adulthood following the neonatal arterial switch operation for transposition of the great arteries. While PEARS surgery is not being performed on young children, it is possible that some adolescents may benefit and potentially so too will a population of children having surgery for congenital heart disease who subsequently survive into adulthood.

Anesthesia for aortic aneurysm surgery

The preoperative assessment should elucidate the extent of the lesion being repaired, as well as associated cardiovascular lesions such as aortic and mitral valve regurgitation, which commonly accompany connective tissue causes of aortic aneurysm. Review of imaging studies is crucial; all patients will have echocardiography, but MRI and/or CT scanning are invaluable in defining the size and extent of the aneurysm, and the properties of any aortic dissection. The non-cardiovascular lesions that accompany the various causes of aortic aneurysm, including genetic syndromes such as Marfan syndrome and inflammatory conditions such as autoimmune or infective disorders, should be investigated. A significant percentage of pediatric cases will involve repeat sternotomy, as associated lesions, such as MR in Marfan syndrome, which presents earlier in life than aortic aneurysm, may have already required repair. Valve-sparing procedures for aortic root replacement in young children will have a moderate rate of medium- to long-term complications, such as aortic regurgitation, that will require reoperation. A recurrent aneurysm is rare and may involve suture lines or more distal aorta with the progression of underlying disease. The complex interaction of aortic valve function with the aortic root means that revision surgery for aortic regurgitation may involve the whole aortic root rather than just the valve leaflets. The usual preparation for repeat sternotomy should be considered, such as planning for the possibility of instituting CPB via peripheral cannulation before opening the chest or in an emergency fashion if required during sternotomy, with appropriate access for rapid resuscitation with blood products and external defibrillation pads in place.

Many pediatric patients undergoing aortic root surgery will be older children, in contrast to the large proportion of pediatric cardiac surgeries, which are done in the first year of life (the majority of cases in many specialized pediatric centers). These older children are often systemically well and asymptomatic, having had the size and rate of expansion of the aorta monitored for many years. Careful preparation includes managing patient and parental anxiety and informing them of plans for postoperative care, including options for adequate pain control.

The cardiovascular status of the pediatric patient scheduled for aortic root replacement will usually depend on associated valve lesions. Patients with Marfan syndrome and other connective tissue disorders are likely to have been treated with beta-blockers. Care should be taken to avoid beta-blocker withdrawal syndrome, which may complicate the postoperative course. The sympathetic overactivity associated with beta-blocker withdrawal is a particular hazard in the early postoperative phase when catastrophic bleeding and suture line dehiscence might be induced. Cautious maintenance of beta-blockade throughout the perioperative period is a reasonable strategy. Given the possibility of a long cross-clamp time, and the resultant decrease in intrinsic inotropy, some anesthesiologists will choose to have an esmolol infusion available and use it as required rather than commit to a longer-acting beta-blocker in this instance. Angiotensin II receptor blockers (e.g., losartan) may be withheld on the morning of surgery, due to the risk of hypotension in the immediate postoperative period.

Hypertension should be avoided both pre- and post-bypass. Pre-bypass, it may cause rupture of the aneurysm, and post-bypass, it may cause excessive bleeding and dehiscence of suture lines. Patients with associated aortic and/or mitral regurgitation may have a dilated left ventricle. Occasionally, this will be associated with poor inotropic function, which will be exacerbated by myocardial ischemia associated with prolonged cross-clamp time. Appropriate inotropic support should be provided along with strategies to minimize afterload whilst maintaining an adequate coronary perfusion pressure. More commonly, patients with preoperative regurgitant valve lesions and a dilated left ventricle with the good left ventricular function will have issues of a large stroke volume after the regurgitant lesions are repaired, and avoidance of hypertension may require postoperative vasodilator therapy along with careful attention to adequate analgesia and sedation.

The association of aortic root replacement procedures with reimplantation of the coronary arteries requires careful assessment of the postoperative electrocardiogram in multiple leads to diagnose ischemic complications that may arise from technical issues with the reimplantation as well as air after removal of the cross-clamp, creating a temporary obstruction of the coronary arteries. Coronary flow can be assessed with TEE or epicardial echocardiography. Coronary artery anastomoses may be a source of bleeding, along with extensive aortic suture lines, and therefore the use of an antifibrinolytic agent is usual practice in these cases.

Marfan syndrome is associated with lung abnormalities that are associated with spontaneous pneumothorax. Positive pressure ventilation may cause the rupture of these lesions. The risk of iatrogenic pneumothorax should be minimized

by avoiding inappropriately high ventilator pressures or volumes. A high index of suspicion for pneumothorax should be maintained if ventilator or cardiovascular problems arise.

Perioperative TEE plays a key role during surgery for aortic root replacement with aortic valve preservation. The often-complex surgical plans involving detailed remodeling of the aortic annulus, the curvature of the aortic root, the size of the sinotubular junction, and the position of the aortic valve leaflets in relation to these structures mean that pre-bypass review of the anatomy and post-bypass review of the repair can provide crucial information regarding the need for immediate revision of a suboptimal surgical result. The ready availability of 3-dimensional TEE in many specialized centers has only enhanced the real-time ability to accurately characterize the pre- and post-repair anatomy in these situations.

KEY POINTS: ANESTHESIA FOR CHILDREN WITH AORTIC ANEURYSM AND AORTOPATHY

- Aortic aneurysms are rare in young children and most commonly affect the aortic root and the ascending aorta.
- Aortopathy in the setting of CHD is of growing concern as more patients survive into adulthood.
- Patients with aortic dilatation will usually be treated with beta-blockers and/or angiotensin II receptor blockers.
- Surgery for aneurysm of the aortic root in children most commonly involves "valve-sparing" techniques, which aim to preserve function in a native aortic valve.
- Control of blood pressure is a key requirement during surgery for patients with an aortic aneurysm to minimize the risk of pre-bypass rupture and prevent early postoperative bleeding and suture line dehiscence.

Mediastinal masses

Masses arising in the anterior mediastinum are likely to involve the great vessels and tracheobronchial tree as they expand. This can have grave consequences, as anesthesia-induced changes in the geometry of the mediastinum may produce complete obstruction of the airway or circulation, causing cardiac arrest. This will be the main focus of the following sections. Although masses arising in the posterior mediastinum can exert mass-effects involving the airway and present a range of challenging anesthesia issues, such as catecholamine secretion (neuroblastomas) and the risk of massive hemorrhage during surgical resection, they do not appear to have the risk of catastrophic respiratory or cardiovascular obstruction that may occur with anesthesia for patients with an anterior mediastinal mass, even if there is some encroachment on the trachea. This may be due to these posterior mediastinal tumors' tendency to displace rather than encase the trachea, as occurs with anterior mediastinal masses.

Incidence, anatomy, and natural history of mediastinal masses in children

The mediastinum is a complex area of the thoracic cavity containing most of the important thoracic structures, excluding the lungs. The compartments within the mediastinum are defined in terms of their relationship to the pericardium as superior, anterior, middle, and posterior, although there are multiple classification systems all of which are subtly different. The middle mediastinum is essentially the pericardium and its contents. The anterior and superior compartments of the mediastinum are not separated by any physical anatomical barrier and some classifications, such as in radiology, merge the anterior and superior compartments into a single anterior mediastinum [129]. This classification is usually used when anterior mediastinal masses are referred to in the anesthesia literature. More recently, there has been a collaborative attempt by the International Thymic Malignancy Interest Group to define a CT-based guideline to make interdisciplinary reporting and diagnosis more easily translatable between specialties [130].

Hodgkin's and non-Hodgkin's lymphoma (NHL), leukemias, teratomas, and germ cell tumors arising from the anterior mediastinum account for more than half of all mediastinal masses. Neuroblastoma, ganglioneuroma, and neurofibroma, arising from the sympathetic chain and nerve roots in the posterior mediastinum account for about a quarter of mediastinal masses and a wide variety of rare diagnoses account for the remainder. These include other tumors, inflammatory processes, congenital anomalies (such as a bronchogenic cyst or esophageal duplication cyst) and, in some series, can include vascular anomalies, such as double aortic arch, seen as an expansion of the mediastinum on plain chest x-ray [131].

Diagnosis of anterior mediastinal masses

Clinical presentation, particularly duration of symptoms and associated features of fever and weight loss, combined with imaging (plain chest x-ray, CT scan, echocardiography) and blood tests, looking for blast cells or tumor markers, will often provide a narrow differential diagnosis. If the mass is a tumor, tissue diagnosis will nearly always be critical to creating a treatment plan. Many of these tumors have an excellent prognosis, but the optimum treatment protocols are very specific to the type and subclassification of the tumor, especially so in the case of leukemias/lymphomas.

Expert oncological advice can lead to sophisticated means of obtaining a diagnosis by relatively non-invasive methods, which may avert the need for anesthesia or allow the use of lower-risk techniques rather than general anesthesia and open surgical biopsy. The anesthesiologist's concern about the risks of anesthesia in a patient with a mediastinal mass must be carefully integrated with the risks of all the strategies available and the clinical information about what the tumor is likely to be. The anesthesia risk seems related to the size and position of the mass as well as the anesthesia/sedation/analgesia technique used, but convincing data about the incidence of cardiovascular or respiratory disaster with anesthesia is lacking. Series published from various institutions looking retrospectively at their morbidity and mortality from anesthesia for diagnosis of mediastinal masses all

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suffer from the bias that patients deemed too high risk to anesthetize were pre-treated with steroids before undergoing anesthesia, so a true incidence of anesthesia complications is not possible to ascertain. It is possible that patients treated with steroids, chemotherapy, or (historically) radiation due to the perceived anesthesia risk, prior to making a tissue diagnosis, may be condemned to suboptimal oncologic treatment which is hard to quantify in a disease that has a high rate of cure. Tumors that do not respond to steroids, such as teratomas, will not be reduced in size by this strategy. Some tumors, such as NHL, are so sensitive to initial therapy that biopsy after this may only reveal non-diagnostic necrotic tissue. However, in most published series tissue diagnosis was possible in more than 90% of cases after pre-treatment with steroids and in cases where it was not possible, the duration of steroid treatment prior to biopsy had been longer. [132–134] Clearly, however, it would be catastrophic if the patient were to die during anesthesia in an attempt to make the diagnosis. The major advance in this area has been an appreciation that with early application of multidisciplinary planning, involving oncologist, anesthesiologist, and proceduralist (surgeon or interventional radiologist), to obtain the diagnosis with the most minimal intervention, only a small minority of these patients with very high-risk compression and no means of obtaining a diagnosis by relatively non-invasive means will be managed with pre-treatment. Most of these will be younger children with significant airway compression and a clinical diagnosis of probable NHL.

Planning the least invasive method for making a diagnosis should be tailored to the patient's clinical findings. Blood sampling may reveal blast cells or tumor markers (e.g., with germ cell tumors). Pleural effusion may be easily sampled and very sensitive techniques such as polymerase chain reaction can identify specific tumor nucleic acid sequences in samples that may not have diagnostic cells on microscopy. The patient may have lymph nodes that are easily accessible for biopsy or excision under local anesthesia (potentially with sedation). Bone marrow biopsy is positive in a significant proportion of patients with NHL, but only in a small minority with Hodgkin's lymphoma. Large mediastinal masses often provide an easy target for image-guided needle biopsy that may not require formal general anesthesia. Ultrasound guidance may be adequate and can allow the procedure to be done in an operating room rather than in a CT scanner [135]. Only a small minority of patients will require a thoracoscopic or open procedure to sample an anterior mediastinal mass. A suggested algorithm for obtaining a diagnosis in a new mediastinal mass is presented in Figure 31.36.

Screening for mediastinal mass prior to undertaking anesthesia in patients with possible lymphoma in other parts of the body is a sensible precaution and should include a plain chest x-ray as a minimum first step. There have been complications related to undiagnosed anterior mediastinal mass in patients having anesthesia for biopsy of a lesion that was suspected to be lymphoma. If lymphoma is a genuine possibility, the patient may be better served by referral to a specialist pediatric oncology unit prior to biopsy, rather than undergoing biopsy in an institution with less-specialized services.

Pathophysiology

The anterior mediastinum is shallow inferiorly and crowded with the trachea and great vessels in the superior aspect. Tumors in this position are restricted by the sternum anteriorly and the pericardium posteriorly. The path of least resistance to growth is around the base of the heart and great vessels, anterior to the trachea and bronchi. The tendency is to surround these structures anteriorly and laterally before they are encased. It is important to note that it is not just the

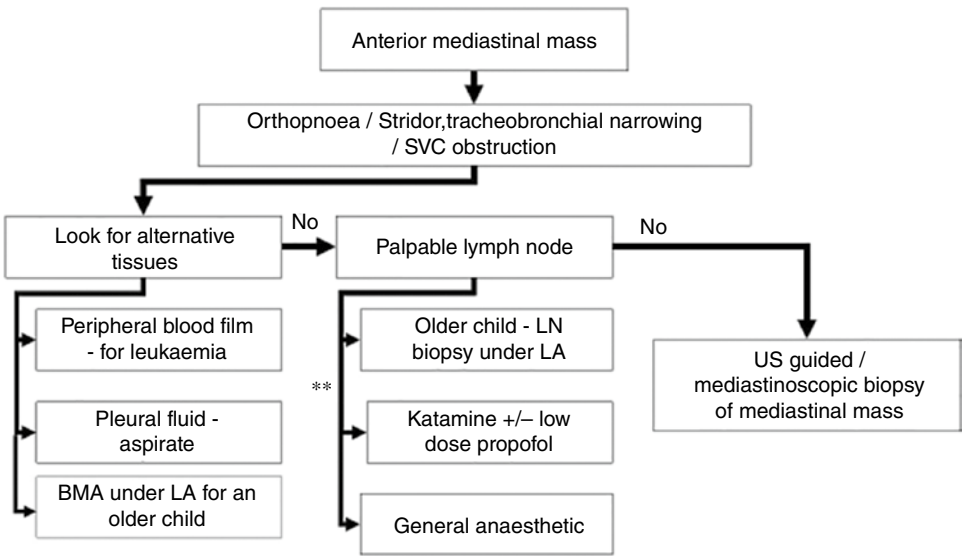


Figure 31.36 Pathway for safe approach for diagnosis of anterior mediastinal mass. Stepwise pathway selecting alternative tissues for diagnosis when available; use of local anesthetic and/or ketamine for peripheral lymph node biopsy, followed by mediastinal access under general anesthesia in very few cases where other options are not feasible. (Source: Malik et al. [132]. Reproduced with permission of Elsevier.)

tracheal part of the airway that might be compressed and that bronchial compression, including bilateral bronchial compression, may be possible. This is of great importance, as not all cases with anterior mediastinal mass where acute airway obstruction is provoked by anesthesia will see the airway obstruction overcome with a rigid bronchoscope.

Catastrophic airway or circulatory complications have been described in case reports of patients with anterior mediastinal masses under anesthesia; however, the mechanism remains uncertain. Case series from major centers have seen respiratory complications occur in about 10–20% of cases anesthetized, but those complications have usually been relatively minor, without long-term consequences. A number of centers did not anesthetize higher-risk patients. [136–138]

All of these reports emphasize efforts to make the diagnosis by minimally invasive techniques and the fact that local anesthesia and selected sedation and analgesia with spontaneous ventilation will allow most diagnostic procedures to be performed. None of the case series has a report of catastrophic airway or circulatory problems under local anesthesia. In one series, there was one patient (not sedated or anesthetized) who received a brief cardiac massage when their airway became obstructed on lying supine in a CT scanner. The case series data support the concept that masses creating more respiratory obstruction and symptoms are more dangerous. However, there have also been case reports of catastrophic complications both in patients with apparently low-risk masses and in those receiving what should be low-risk sedation/analgesia techniques.

One hypothesis for the mechanism of catastrophic obstructive complications is based on the fact that tumor expansion flattens and holds rigid the encased (or partially encased) airways or vascular structures, creating a ribbon-like cross-section. The well-described changes in lung mechanics at induction of general anesthesia include a loss of functional residual capacity based on the diaphragm moving cranially and changes in chest wall muscle tension. It is quite plausible that this change in conformity of the thorax could completely kink the flattened ribbon-like structures created by tumor compression. This concept has informed practice in selecting anesthesia techniques (preferentially choosing sedation techniques more likely to preserve normal lung mechanics and spontaneous ventilation) for managing these patients and likely accounts for the absence of catastrophic obstruction in series from major institutions.

Anesthesiologists should be aware of the extraordinary rate of expansion of some NHLs. The "doubling time" (average time for a cell division cycle which will double the size of the tumor) may range from as little as 12 hours to a few days. A patient presenting with a mediastinal tumor due to NHL may have very significant disease progression and increased compression of cardiorespiratory structures between the time of initial chest imaging and a subsequent procedure involving anesthesia. This should inform efforts to meticulously review their clinical status for worsening obstructive signs or symptoms, even if they have had reassuring imaging in previous days.

Anesthesiologists should be mindful to avoid the routine use of steroids as antiemetics in these patients. Steroids may cause rapid necrosis of the tumor, which could jeopardize diagnosis, precipitate tumor lysis syndrome, or disturb the current best-practice protocol for curative treatment, potentially worsening prognosis. Tumor lysis syndrome is caused by rapid necrosis of a large tumor when exposed to therapeutic agents, with systemic absorption of the released intracellular contents. Lethal hyperkalemia and renal failure are the most prominent complications and as such, these patients are intensively monitored and managed for tumor lysis syndrome in oncology protocols. Steroid use in a patient with an unsuspected mediastinal mass has been associated with tumor lysis syndrome leading to death.

Surgery for anterior mediastinal masses

Open surgery for the removal of an anterior mediastinal mass is not common in children. Non-lymphomatous tumors and other lesions that cannot be managed medically will, however, likely require surgical resection. The surgical approach will usually be by sternotomy or mediastinoscopy. Mediastinotomy has been used for the biopsy of these lesions, and a technique for doing mediastinotomy with local anesthesia has been described. For some tumors undergoing surgical removal, the use of CPB, although adding complexity and anticoagulation, may allow safer removal of the lesion. Pre-emptive peripheral (e.g., femoral) CPB or ECMO may be indicated in some cases for planned support of respiration and the circulation prior to formal general anesthesia and intubation in a high-risk patient. It should be noted that this scenario is different from the use of CPB or ECMO as a rescue for cardiac or respiratory arrest after induction of anesthesia, which is impractical and should not be considered to be a reasonable management strategy, especially in children.

Anesthesia for patients with an anterior mediastinal mass

Sudden induction of deep general anesthesia in patients with an anterior mediastinal mass may unpredictably cause complete respiratory obstruction or circulatory arrest. Larger symptomatic masses with airway compression are probably at greater risk, but all patients should be treated with caution.

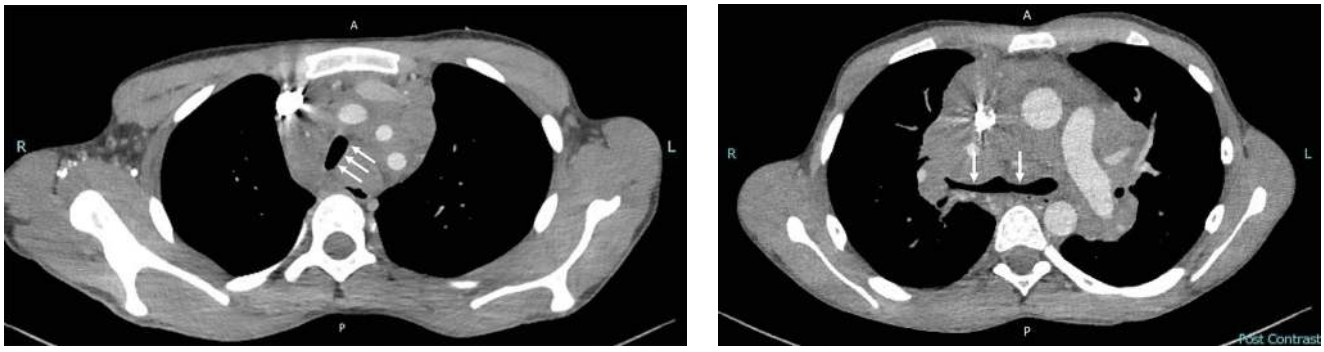
General assessment should occur along with specific history and examination of the patient to assess mass effects and associated conditions. History may reveal dyspnea or stridor, which may be intermittent. A special inquiry should be made as to whether posture affects symptoms. Some patients cannot tolerate lying flat, especially when supine, but may tolerate being prone. Facing one side or another may worsen or improve symptoms. Signs of superior vena cava compression are ominous. These include upper body and facial edema as well as distended, non-pulsatile, jugular veins. The edema may be worse on waking in the morning and regress with upright posture during the day. Pemberton's sign, which involves evoking symptoms and signs of SVC obstruction when patients stretch both arms above their head, may reveal lesser degrees of obstruction and should be actively sought.

The postural relationship of symptoms and signs may be very important not only for planning safe positioning during procedures but also for defining possible safer positions into which a patient might be moved should severe obstruction

arise. Apart from lateral and prone positioning, it has also been suggested that physically pulling the sternum forward may move the tumor away from the airway or heart and great vessels and may relieve acute compression. The fact that arm and shoulder position may increase pressure on the superior part of the anterior mediastinum may be particularly important in positioning for CT scanning and for some surgeries.

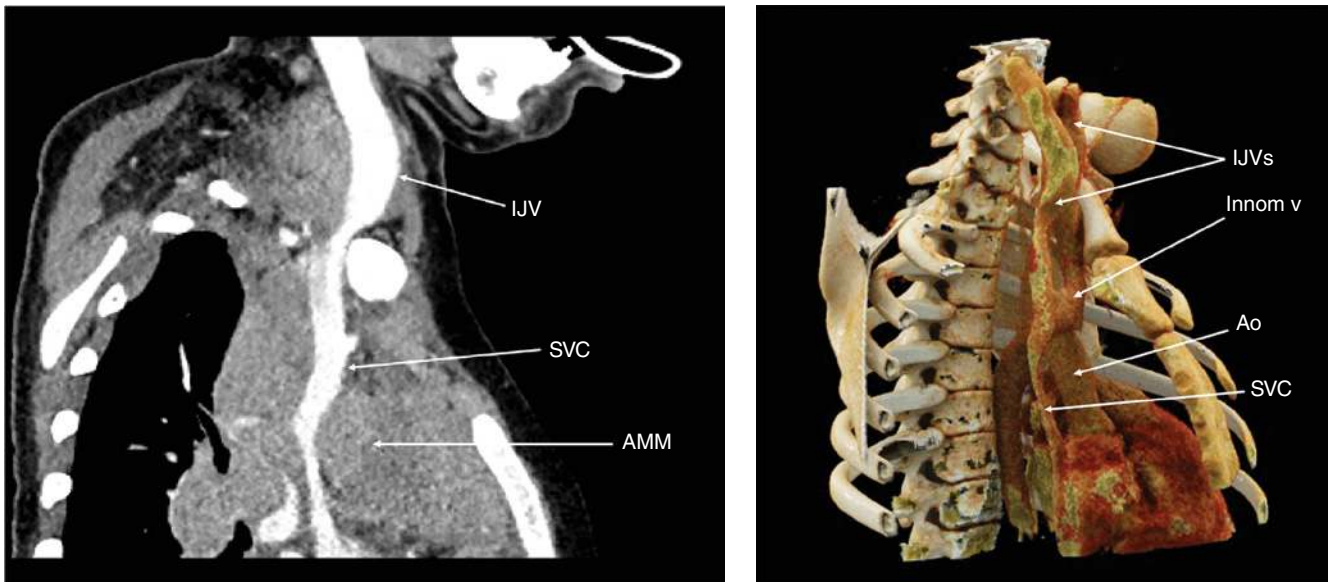
Imaging the chest will provide crucial information. CT scanning is often the technique of choice in symptomatic children, as tolerating the duration and positioning required for an MRI while awake may be impossible. The short time required for CT imaging makes this much more practical, but not without hazard in those children that have difficulty lying flat and putting their arms above their heads, as is usually required for a CT of the chest. A careful review of the CT will outline the degree and extent of compression of the airway, great vessels, and heart. Some CT images are provided showing tracheal, bronchial, and SVC obstruction by tumor. Pleural and pericardial effusions are quite common in these patients, especially those with NHL. Echocardiography will quantify pericardial effusion and should carefully examine the path of the pulmonary arteries, superior vena cava, and right ventricular outflow for obstruction (Figures 31.37 and 31.38).

Widely quoted criteria for critical airway compression in children with anterior mediastinal mass that contraindicate anesthesia are: (i) a 50% reduction in predicted tracheal diameter on CT scan; (ii) a 50% reduction in peak expiratory flow rate on spirometry; (iii) severe narrowing or complete occlusion of one or both main-stem bronchi; or (iv) clinical findings of acute respiratory distress or impending respiratory failure. These points are not robustly defined but have



(A) (B)

Figure 31.37 Tracheobronchial compression by anterior mediastinal mass. (A) Axial computed tomography (CT) image demonstrating tracheal compression and deviation (arrow). (B) Inferior slice in same patient demonstrating bilateral mainstem bronchial compression by the mass (arrows). Source: Courtesy of Department of Medical Imaging, The Royal Children's Hospital, Melbourne.



(A) (B)

Figure 31.38 Compression of superior vena cava (SVC) by anterior mediastinal mass (AMM). (A) Computed tomography (CT) sagittal curved multi-planar reconstruction demonstrating significant multilevel obstruction by a tumor, leading to dilation of SVC and internal jugular veins (IJV). (B) Three-dimensional virtual CT reconstruction showing significant compression of SVC, and dilation of innominate (innom and internal jugular veins. Source: Courtesy of Department of Medical Imaging, The Royal Children's Hospital, Melbourne.

been widely adopted. The original series that promulgated these criteria involved no patient with those criteria being anesthetized (so there is no estimate of the hazard of anesthesia in those who fulfill the criteria), and the modest number (17 in the original paper) [139] who had anesthesia or sedation in whom there was a lack of serious complications adds to data from similar series, but an unacceptably high incidence of serious complications is likely not to be detected in a series that size. Despite this criticism of the detail of the data, the principles on which this group bases management are very sound. The practical points are that biopsies were performed using local anesthesia in most patients deemed at high risk from general anesthesia. They have since added to the series and refined an algorithm for seeking a diagnosis with the most minimally invasive procedures done first. In a latter series of 40 patients with anterior mediastinal mass who fulfilled their criteria for critical airway compression, only two of the patients had therapy without a tissue diagnosis, and, in that series, only three had general anesthesia [136].

Anghelescu et al.'s [139] analysis of 117 patients with a mediastinal mass who were anesthetized, with 11 having respiratory complications of anesthesia, showed that these complications were statistically associated with orthopnea, upper body edema, great vessel compression, and main-stem bronchus compression. Pleural effusion and tracheal compression did not quite reach statistical significance. This group also emphasized the importance of using minimally invasive techniques to make a diagnosis. They modified the anesthesia technique in an attempt to decrease risk, avoiding muscle relaxants and maintaining spontaneous ventilation.

More recently, in an attempt to find a metric that can be used to stratify risk in terms of whether a patient can safely be anesthetized, a group from Japan have recommended using Standardised Tumor Volume, based on calculating the volume of the tumor as if it were an ellipsoid structure and standardizing it for patient height. At this stage, there are no prospective data confirming this new measurement's utility in stratifying for anesthetic risk [140].

Pragmatically, if a patient can tolerate a procedure done with local anesthesia alone, that should be the aim. If systemic agents are required to achieve sedation and analgesia, careful titration aimed at maintaining spontaneous ventilation can avoid most incidents of catastrophic collapse. There are disturbing isolated case reports of cautious techniques still being associated with significant complications, but there are also a large number of case series with careful case selection and modified anesthesia techniques, without serious complication. In association with local anesthesia, various combinations of midazolam, ketamine, and, more recently, dexmedetomidine, perhaps titrated with small boluses and maintained with an infusion, can provide a low risk of major change in conformation of the chest wall and catastrophic cardiorespiratory compression. Spontaneous ventilation and, in many cases, consciousness can be maintained while a procedure is performed. CPAP by face mask may assist with maintaining airway patency during the procedure. Endotracheal intubation is usually avoided. Topical anesthesia to the airway can facilitate intubation in cases where this is required which may assist the maintenance of spontaneous ventilation with modest anesthesia requirements. The addition of opioids if intubation is required can help with the tolerance of the endotracheal tube but can increase the risk of apnea. Very low-dose infusions (e.g., 2 mg/kg/hour) with small boluses (e.g., 0.2 mg/kg) of propofol may be cautiously introduced for similar indications. The principle is that the minimum necessary degree of sedation/anesthesia should be used and boluses or infusion rate changes should be small and incremental. This will minimize the risk of "overshoot" in the depth of anesthesia, perhaps allowing detection of deterioration before a catastrophe occurs, with a good chance of a rapid return to the depth of sedation/anesthesia that was previously tolerated. Most of these sedation/anesthesia strategies involve agents with effects not well monitored by the proprietary depth of anesthesia monitors.

Emergency equipment and appropriately skilled staff should be immediately available to attempt to reverse a situation of respiratory or cardiovascular obstruction/collapse. This may include a rigid bronchoscope and reinforced endotracheal tubes to overcome a compressed trachea. It is notable that some large masses may cause bilateral bronchial compression, and obstruction at that level will not be overcome by these techniques. As noted above, in rare cases, CPB or ECMO support with femoral cannulation under local anesthesia, occurring before the biopsy procedure, is necessary.

KEY POINTS: ANESTHESIA FOR CHILDREN WITH MEDIASTINAL MASSES

- Anterior mediastinal masses can cause lethal airway or cardiovascular compression with general anesthesia.
- A multidisciplinary team in a specialist center should receive an urgent referral of patients with a mediastinal mass.
- Most patients will not require a standard general anesthetic.
- The most minimally invasive method of obtaining a diagnosis should be attempted prior to contemplating anesthesia.
- Local anesthesia should be used alone or combined with sedation/analgesia/anesthesia to minimize requirements for systemic agents.
- CPB or ECMO may have a pre-emptive role in rare cases of high-risk mass, where it is initiated after preparation for cannulation is done under local anesthesia, with the patient awake or receiving sedation.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

17 Choi S, Lawlor C, Rahbar R, Jennings R. Diagnosis, classification, and management of pediatric tracheobronchomalacia: a review. JAMA Otolaryngol Head Neck Surg 2019;145:265–275. An excellent comprehensive review of the diagnostic workup, organization and classification, and surgical planning of conditions leading to tracheobronchomalacia including vascular rings and slings.

25 Backer CL, Kelle AM, Mavroudis C, et al. Tracheal reconstruction in children with unilateral lung agenesis or severe hypoplasia. Ann Thorac Surg 2009;88:624–31. An excellent explanation of the

technique of slide tracheoplasy and tracheal resection and reanastomosis with the use of CPB, with excellent illustrations of the anatomy and surgical procedures.

50 Imamura M, Dossey AM, Jaquiss RD. Reoperation and mechanical circulatory support after repair of anomalous origin of the left coronary artery from the pulmonary artery: a twenty-year experience. Ann Thorac Surg 2011;92:167–72. A case series of ALCAPA repairs focusing on requirement for mechanical circulatory support, and short- and long-term outcomes in this challenging group of patients.

61 Burch TM, McGowan FX Jr, Kussman BD, et al. Congenital supravalvular aortic stenosis and sudden death associated with anesthesia: what's the mystery? Anesth Analg 2008;107:1848–54. A comprehensive review of the anatomy and pathophysiology of, and surgical and anesthetic approaches to, supravalvular aortic stenosis, with a focus on abnormal coronary artery anatomy and obstruction, which is frequently out of proportion to the degree of aortic stenosis.

68 Kuhn B, Peters J, Marx GR, et al. Etiology, management and outcome of pediatric pericardial effusions. Pediatr Cardiol 2008;29:90–4. A well-written review article focusing on all aspects of the etiology, anatomy, pathophysiology, and management of pericardial effusions.

94 Henaine R, Roubertie F, Vergnat M, Ninet J. Valve replacement in children: a challenge for a whole life. Arch Cardiovasc Dis 2012;105:517–28. A comprehensive modern review article of all valve replacements in children, containing an extensive section on mitral valve replacement: indications, techniques, and outcomes.

104 Gregory SH, Sodhi N, Zoller JK, et al. Anesthetic considerations for the transcatheter management of mitral valve disease. J Cardiothorac Vasc Anesth 2019;33:796–807. A comprehensive review of anesthetic management considerations for transcatheter treatment of mitral valve disease; this approach serves as a model for congenital heart disease invasive transcatheter valve interventions on mitral and other valves.

114 Niwa K. Aortic dilatation in complex congenital heart disease. Cardiovasc Diagn Ther 2018;8:725–738. A comtemporary comprehensive review of the many congenital heart diseases that lead to aortic dilation, their diagnosis, management, and surgical treatment.

128 Pepper J, Golesworthy, T, Izgi C, et al. Personalised external aortic root support (PEARS) to stabilise an aortic root aneurysm. Br J Cardiol 2020;27:87–92. A comprehensive description of a new and novel procedure to stabilize aortic root aneurysms with the goal of preventing futher progression, and minimizing future interventions.

137 Anghelescu DL, Burgoyne LL, Liu T, et al. Clinical and diagnostic imaging findings predict anesthetic complications in children presenting with malignant mediastinal masses Paediatr Anaesth 2007;17:1090–8. A series of 117 patients with a mediastinal mass who were anesthetized, with 11 having respiratory complications of anesthesia. Complications were statistically associated with orthopnea, upper body edema, great vessel compression, and main-stem bronchus compression.

CHAPTER 32

Anesthesia for Cardiac and Pulmonary Transplantation

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Heart transplantation

Following the pioneering adult and infant heart transplants of the late 1960s [1, 2], cardiac transplantation has evolved into a successful, standard therapy for end-stage pediatric heart disease. Advances in immunosuppressant therapy, pretransplant recipient optimization, donor organ procurement/preservation techniques, and post-transplant recipient management have all contributed to improved pediatric outcomes despite increased case complexity [3]. The Scientific Registry of the International Society for Heart and Lung Transplantation (ISHLT) is the main source of international multicenter data and captures approximately 75% of worldwide thoracic transplant activity [3]. Currently, approximately 500–600 pediatric heart transplants are performed annually across the globe, with 210 pediatric centers reporting data to ISHLT [3] (Figure 32.1). Most of the pediatric data are reported from centers in Europe and North America. Centers performing >10 transplants/year perform the majority (nearly 50%) of transplants [4] (Figure 32.2).

Diagnostic indications for heart transplantation

Diagnostic indications for pediatric heart transplantation were updated in 2007 [5] and summarized in recent ISHLT annual reports [4, 6]. As post-transplant survival rates and outcomes have improved, the dilemma is no longer whether to transplant, but rather when to do it [7]. Premature transplantation results in exposure of the recipient to the hazards of transplantation and immunosuppression. Excessive delay may result in death without transplantation or the development of high-risk comorbidities, such as renal and liver dysfunction, malnutrition, and elevated pulmonary vascular resistance (PVR). Optimal timing for listing will vary depending on the primary diagnostic indication and anticipated disease progression.

Primary diagnostic indications for heart transplantation are categorized into four main groups, with dilated cardiomyopathy (DCM) and congenital heart disease (CHD) accounting for the majority of pediatric heart transplants (Table 32.1) [6]. Indications for heart transplantation vary with age; the majority of transplants in infants

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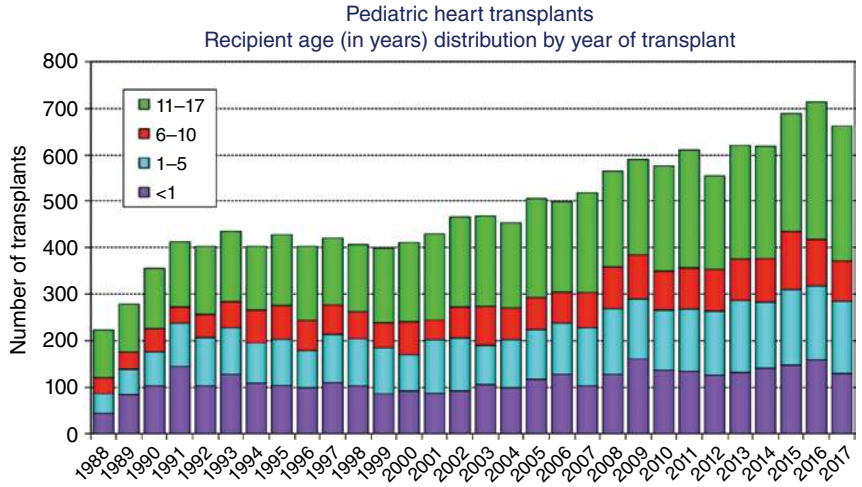


Figure 32.1 Number of pediatric heart transplants performed per year – age distribution by year of transplant. Note that this figure includes only the heart transplants that are reported to the International Society for Heart and Lung Transplantation Transplant Registry. (Source: Rossano et al. [4]. Reproduced with permission of Elsevier.)

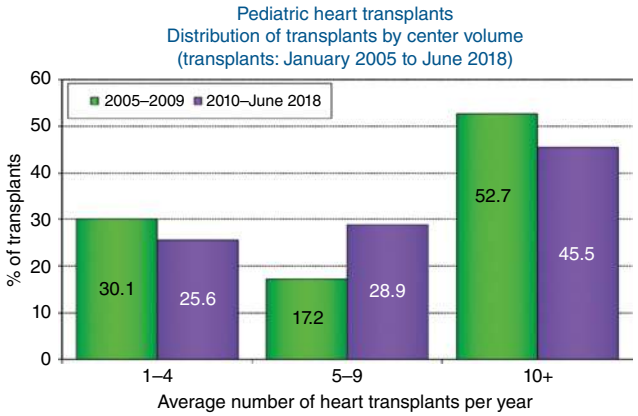


Figure 32.2 Pediatric heart transplants: distribution of heart transplants by center volume. (Source: Rossano et al. [4]. Reproduced with permission of Elsevier.)

Table 32.1 Primary diagnostic indications for pediatric heart transplants

Category (abbreviation)	Diagnoses in category
Congenital heart disease (CHD)	Congenital heart defect: HLHS – unoperated; with surgery; without surgery; previous surgery unknown; or valvular heart disease
Dilated cardiomyopathy (DCM)	Dilated myopathy due to: adriamycin; alcohol; familial; idiopathic; myocarditis; postpartum; viral; or other reasons
Retransplant (RETX)	Retransplant due to: acute rejection; chronic rejection; coronary artery disease; hyperacute rejection; nonspecific; primary failure; restrictive/constrictive causes; or other reasons
Other (OTHER)	Arrhythmogenic right ventricular dysplasia; cancer; coronary artery disease; myopathy-ischemia; hypertrophic cardiomyopathy; muscular dystrophy; restrictive cardiomyopathy (any reason); or other cardiac disease

Source: Rossano et al. [6]. Reproduced with permission of Elsevier.
HLHS, hypoplastic left heart syndrome.

are for CHD, whereas DCM is the leading cause in children >1 year of age [4, 8] (Figure 32.3). Indications for heart transplant also vary with geography (Figure 32.4), such that the primary diagnosis in Europe and other countries is DCM. CHD is a more common indication in North America than in Europe, accounting for 43% of heart transplants in North America versus 22% in Europe. Diagnostic indications for heart transplant are important since they are associated with differences in post-transplant morbidity and mortality. For example, DCM confers a post-transplant survival advantage compared with CHD across all age groups [4].

Mechanical circulatory support as a bridge to transplant is being increasingly used in children for all diagnostic indications. Approximately 30% of patients are currently bridged to transplant with a ventricular assist device (VAD) and approximately 3–5% with extracorporeal membrane oxygenation (ECMO) [4].

Dilated cardiomyopathy

Almost 40% of children presenting with symptomatic DCM receive a heart transplant or die within 2 years of diagnosis [8]. Over 50% of children ≥5 years of age with DCM are bridged to transplant with a VAD [4]. *DCMs* have a diverse spectrum of etiologies and phenotypic manifestations (Table 32.2). Pediatric myocarditis, a secondary cause of DCM, has a 50–80% chance of resolution within 2 years of diagnosis even when patients present with acute, severe symptomatology [9, 10].

Congenital heart disease

CHD as a primary indication for heart transplant includes a diverse group of conditions and accounts for 20–60% of pediatric heart transplants depending on age and geographical

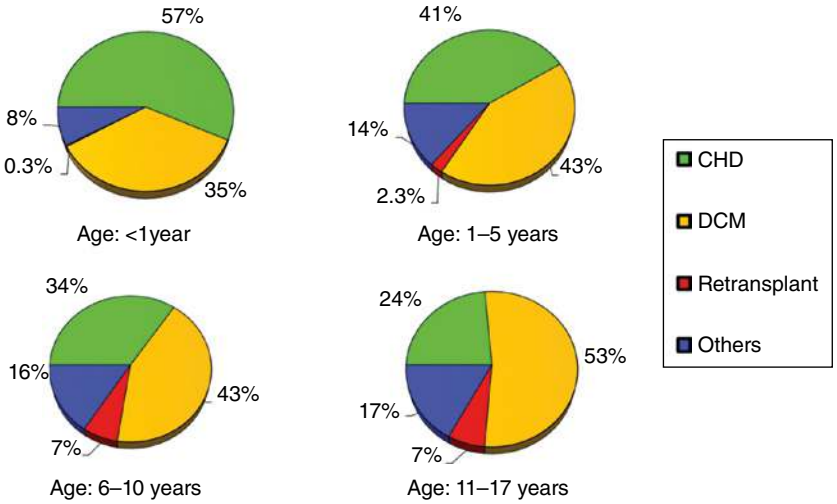


Figure 32.3 Pediatric heart transplants: recipient diagnosis by age, 2010–2018. (Source: Rossano et al. [4]. Reproduced with permission of Elsevier.)

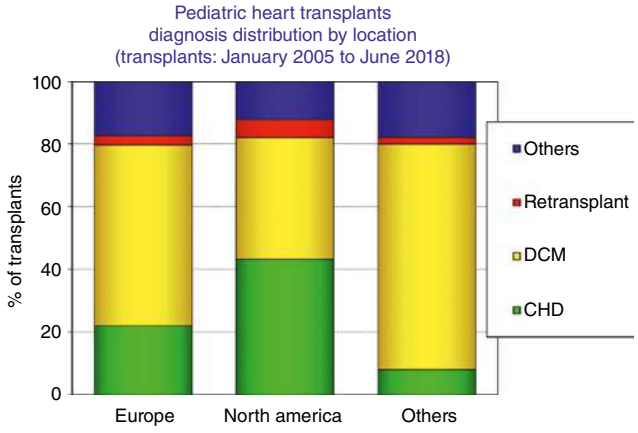


Figure 32.4 Pediatric heart transplants: diagnosis distribution by geography. (Source: Rossano et al. [4]. Reproduced with permission of Elsevier.)

location (Figures 32.3 and 32.4). With improved outcomes and widespread adoption of the neonatal stage I palliation, the number of neonates and infants with single ventricle physiology undergoing heart transplant as a primary therapeutic modality has decreased significantly. However, there is an increasing number of patients presenting later in life with failing single ventricle palliation and this subgroup constitutes at least two-thirds of patients with CHD presenting for heart transplant [11, 12]. Failing Fontan patients are a growing cohort presenting for pediatric heart transplant and are discussed in more detail later.

Other indications

"Other indications" are primarily due to hypertrophic cardiomyopathies (HCM) and restrictive cardiomyopathies (RCM).

HCMs account for 5–6% of pediatric heart transplants and include several genotypes and etiologies including idiopathic, familial inborn errors of metabolism, and malformation syndromes such Noonan's and Beckwith–Wiedemann syndromes. [5]. HCM is a leading cause of sudden cardiac death in adolescents and young adults. A recent independently validated model for risk of sudden cardiac death in pediatric HCM identified a positive associated with nonsustained ventricular tachycardia and unexplained syncope and a nonlinear association with age at diagnosis, interventricular septal thickness z score, left ventricular (LV) posterior wall diameter z score, and left atrial diameter z score [13].

RCMs result in diastolic dysfunction usually with normal ventricular size and function and biatrial enlargement. One-third of patients have a mixed phenotype of RCM and HCM [14]. RCMs are associated with myocardial infiltrative processes, such as amyloidosis, hemochromatosis, glycogen storage disease, mucopolysaccharidosis, sarcoidosis, and endomyocardial fibrosis. Syncope and ischemia indicate a poor prognosis, and elevated PVR is often present. Due to limited medical and surgical treatment options and the risk of irreversible pulmonary hypertension, thromboembolic disease, and sudden death many centers favor an approach of early listing for heart transplant [5].

Retransplantation

Retransplantation accounts for a small percentage (5–7%) of pediatric heart transplants and is more common in North America (6%) than Europe (2%) [4, 15]. Coronary allograft vasculopathy (CAV), the most common indication for retransplantation, is discussed in more detail later. Other indications include acute or chronic rejection and primary graft failure (Table 32.3). Data indicate that retransplantation for early primary graft failure has a worse prognosis than for late graft failure or CAV [16–18]. The best outcomes are associated with those retransplanted for CAV [15, 18]. Children with graft failure due to acute rejection with hemodynamic compromise, especially <6 months post-transplant, are regarded as inappropriate candidates for retransplantation [18]. The majority (65%) of pediatric retransplants occur at least 3 years after the primary transplant [4, 15]. Retransplantation has a similar 1-year survival to primary transplants but is associated with

Table 32.2 Causes of dilated cardiomyopathy

Primary DCM
Familial/genetic
Sarcomeric
Mitochondrial diseases
Neuromuscular disorders
Laminopathies
Secondary DCM
Inflammatory
Toxins
Iron
Lead
Cobalt
Arsenic
Anthracycline
Radiation
Metabolic disorders
Endocrinopathies
Thyroid disorders
Catecholamine-secreting tumor
Parathyroid disease
Diabetes mellitus
Fatty acid oxidation disorders
Carnitine deficiency
Malonyl coenzyme decarboxylase deficiency
GSDs
GSD type II (Pompe disease)
GSD type IV (Andersen disease)
Lysosomal storage disorders
Gaucher disease
Mucopolysaccharidoses
Sphingolipidoses
Nutritional disorders
Thiamine deficiency
Selenium deficiency
Protein energy malnutrition
Structural heart diseases
Valvular heart disease
Ischemia: coronary artery anomalies, coronary artery injury
Single ventricle
Pulmonary diseases

Source: Lipshultz et al. [8]. Reproduced with permission of Wolters Kluwer Health, Inc.
DCM, dilated cardiomyopathy; GSD, glycogen storage disease.

Table 32.3 Indications for cardiac retransplantation

	No.	%
Acute rejection	19	9
Hyperacute rejection	7	3
Coronary allograft vasculopathy	111	51
Chronic rejection	16	7
Nonspecific graft failure	34	16
Primary failure	10	5
Other	22	10

Source: Mahle et al. [17]. Reproduced with permission of Elsevier.

decreased long-term survival and increased transplant-related morbidities such as renal dysfunction, late rejection, and CAV [4, 15, 18].

KEY POINTS: HEART TRANSPLANTATION

- The number performed per year in the United States is limited primarily by donor organ availability.
- The commonest indication for transplantation in infants is CHD.
- The commonest indication in older children is cardiomyopathy.
- Diagnostic indications have an important impact on post-transplant outcomes.
- Currently, approximately 30% of recipients are bridged to transplant with a VAD.

ABO-incompatible heart transplantation

Infants listed for heart transplant have the longest waitlist time and a higher waitlist mortality when compared with older children. Infant waitlist mortality in the United States is 25% compared with 15% for children and adolescents [19, 20]. An increasing number of centers are adopting ABO-incompatible (ABO-I) heart transplants as a standard practice to reduce waitlist mortality in this vulnerable population. Historically donor and recipients are matched for ABO compatibility. ABO-I heart transplants have been avoided because of the risk of hyperacute rejection that can occur when recipient isohemagglutinins (serum anti-A or anti-B antibodies) bind to the corresponding blood group antigens on donor organ vascular endothelium. Organ allocation across blood group barriers increases the donor organ pool available for heart transplantation. Since blood group O-type recipients have both anti-A and anti-B antibodies (isohemagglutinins), only an O-type donor is compatible and hence they have the longest waitlist time. Isohemagglutinins are not present at birth, and serum antibody titers remain low until 12–14 months of age [21]. Young infants also have an immature complement system. Therefore, the mechanisms leading to hyperacute rejection in ABO-I heart transplant are absent during infancy. This discovery was pioneered in Toronto in 1996 when the first ABO-I heart transplant was performed [22]. With increasing multicenter experience and data, current United Network for Organ Sharing (UNOS) guidelines recommend ABO-I heart transplant in children under 1 year of age with any isohemagglutinin titer and in 1–2 years with titers less than 1 : 16. In 2016, UNOS also changed its allocation criteria so that patients listed as ABO-I have equal organ priority to ABO-compatible (ABO-C) heart transplants. This has led to an increased number of patients listed and receiving ABO-I heart transplants. Various registry and multicenter data have shown comparable survival and outcomes for ABO-I heart transplants compared with ABO-C heart transplants in infants <1 year and no difference in rates of rejection 1-year post-transplant [23]. There is consistent data that ABO-I heart transplants decrease waitlist time, especially in patients with blood group O [23, 24].

Recipient evaluation

A detailed assessment of patients is required to determine their suitability for heart transplantation (Box 32.1). Factors that must be considered include severe central nervous system, liver or kidney dysfunction, pulmonary infarction, pulmonary hypertension, morbid obesity, and some infections, malignancies, or chromosomal abnormalities. Prediction of mortality after transplantation was more accurate when multiple high-risk criteria were included in the assessment of potential recipients [25].

Transplant centers usually have formal meetings to present a structured multidisciplinary evaluation of recipients prior to accepting for heart transplant listing. At Stanford Children's Hospital, a cardiac anesthesiologist is present at these meetings. Evaluation revolves around four key areas [5]:

1. Comprehensive assessment of cardiovascular system (CVS) anatomy and hemodynamics
2. Assessment of end-organ dysfunction and chronic noncardiac disease including nutritional status
3. Human leukocyte antigen (HLA) sensitization
4. Psychosocial evaluation of patient and patient's family

Box 32.1: Routine precardiac transplant evaluation

History and physical examination
- Age, height, weight, body surface area
- Diagnoses
- Past medical history
- Medications
- Allergies
- Immunization record

Laboratory data
- Liver and kidney function tests
- Urine analysis
- Glomerular filtration rate
- Prothrombin time/INR/partial thromboplastin time
- Complete blood count and differential
- PPD skin test
- Serologies for human immunodeficiency virus, hepatitis, cytomegalovirus, Epstein–Barr virus, *Toxoplasmosis gondii*, syphilis
- ABO type
- Panel-reactive antibody

Cardiomyopathy workup
- Thyroid function tests
- Blood lactate, pyruvate, ammonia, acyl carnitine
- Urine organic acids, acyl carnitine
- Skeletal muscle biopsy
- Karyotype

Cardiopulmonary data
- Cardiac catheterization
- Echocardiogram
- Radionuclide angiography
- Endomyocardial biopsy
- Electrocardiogram
- Chest radiograph
- Pulmonary function tests
- VO_{2max}

Psychosocial evaluation
- Possible relocation
- Long-term supportive care
- Parental substance abuse
- History of neglect or abuse

Consultations as required
- Dental services
- Other services

It may be necessary to repeat some tests if the patient's medical status changes over time. INR, international normalized ratio; PPD, purified protein derivative.

Source: Adapted from Shaddy and Parisi [8].

CVS anatomy and hemodynamics

Assessment of cardiopulmonary function usually includes cardiac catheterization and magnetic resonance imaging (MRI) or computed tomography (CT) to delineate the vascular connections, particularly in patients previously palliated for complex heart disease. Abnormal cardiovascular anatomy influences surgical technique during harvesting and transplantation. For example, a patient with palliated hypoplastic left heart syndrome and residual arch obstruction may require extra donor arch material during donor harvesting, or a Fontan patient with branch proximal pulmonary artery (PA) stenosis may need PA reconstruction during transplantation. Identifying anomalous systemic or pulmonary venous return, PA malformations, and accessory collateral pulmonary blood flow is also important for the surgical procedure [5].

Quantifying PVR prior to listing is important because PVR > 6 Wood Units/m^2 or a transpulmonary gradient >15 mmHg is associated with acute right heart failure and increased mortality [26, 27]. The upper limit of PVR associated with successful cardiac transplantation has not been established in children. All patients with pulmonary hypertension have PVR measured at baseline conditions and during administration of oxygen, nitric oxide (NO), and/or other pulmonary vasodilator therapy. When the response is marginal, repeat values after 1–2 weeks of inotropic support, afterload reduction, and pulmonary vasodilation may demonstrate improvement. Experienced institutions may accept children with PVR as high as 8–12 Wood Units/m^2 if it is reactive. Patients whose PVR does not respond to therapy may be the candidates for heart–lung transplantation (HLT) or lung transplantation. Children with RCM are particularly prone to marked elevation of PVR, which may contribute to the poor prognosis in these patients and make cardiac transplantation problematic. Nitric oxide appears to be a good agent to demonstrate reversibility of PVR in these patients [26]. PVR also improves after left ventricular assist device (LVAD) implant, especially for patients with DCM and left atrial hypertension [28]. Endomyocardial biopsy may be required prior to listing for dilated cardiomyopathies to identify acute myocarditis and myocardial infiltrates. A diagnosis of acute myocarditis is important in determining suitability for transplant listing since there is chance of resolution as mentioned earlier [9, 10].

End-organ dysfunction/chronic noncardiac disease

Pretransplant end-organ dysfunction and chronic noncardiac disease have an impact on post-transplant morbidity and mortality. Assessing the degree of pretransplant renal dysfunction is important because reduced estimated glomerular

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filtration rate (eGFR) and pretransplant renal dialysis are associated with increased 1-, 5-, and 10-year mortality [4, 29]. Some centers will treat moderate-severe renal dysfunction with a combined heart kidney transplant.

Assessing liver function is also important especially in failing Fontan patients. Elevated serum bilirubin is a continuous risk factor for 1-year mortality post-transplant [12, 29]. There is an increasing trend of treating irreversible liver disease with a combined heart–liver transplant (CHLT) and is discussed in more detail later.

Assessing the degree of chronic lung disease especially in older children with CHD is important and will include pulmonology assessment and pulmonary function tests. Evaluation of patients with cardiomyopathy should include a metabolic workup to detect potential etiologies such as mitochondrial disorders and genetic studies. Transplant teams are also intensifying attention on the pretransplant nutritional status of the recipient since this may have a significant impact on postoperative hemostasis, wound healing, and recovery.

HLA sensitization and immune function

Infectious disease and immune system evaluation are essential. The child's immunization status should be updated if necessary. Tests are performed for latent infections, such as cytomegalovirus or Epstein–Barr virus, that may become clinically significant during immunosuppression. Donor matching is based on ABO typing. The candidate's blood is also screened for antibodies against sera of random blood donors and, if reactive, a serum crossmatch with the donor is performed.

There is an increased risk for graft dysfunction, acute cellular and antibody-mediated allograft rejection, and chronic rejection/CAV after heart transplantation in patients sensitized to HLAs. The number of heart transplant candidates allosensitized to HLA antigens has increased in recent years because of exposure to blood products, homograft material used in surgical palliation of CHD, use of ventricular assist and mechanical support devices, and patients requiring retransplantation. Determinations of panel-reactive antibody (PRA) are done to delineate a patient's potential for sensitization to donor HLA antigens. Patients with a reaction to >10% of antigens (either class I or II) are generally considered to be allosensitized. However, this is allosensitivity to a "random" donor; having a positive crossmatch with the *actual* donor (HLA antibody toward donor alloantigens) at the time of transplant has been clearly demonstrated to increase the risk for poor outcome after transplant. Donor-directed HLA antibodies are associated with rejection-related mortality from cellular and antibody-mediated acute rejection and CAV. Patients with PRA >10% pretransplant and a positive crossmatch are at high risk for graft loss from hyperacute rejection and early acute cellular rejection (ACR), which in turn increase the risk of CAV.

Allosensitized patients may be excluded from heart transplant, restricted to certain donors, or experience prolonged waiting times. Some transplant programs require a prospective negative donor-specific crossmatch for patients with PRA screens >10%. However, this approach is problematic because of the donor shortage and some patients have antibodies to many HLAs. Therefore, perioperative management protocols for HLA-sensitized children have been developed and include pretreatment of sensitized patients (using treatments such as intravenous immune globulin, cyclophosphamide, mycophenolate mofetil [MMF], and rituximab), intraoperative plasma exchange, post-transplant plasmapheresis, and T- and B-cell suppression [30–34].

Psychosocial evaluation of patient and patient's family

Heart transplantation requires long-term immunosuppression, frequent invasive procedures, and lifelong medical care. Patients must live close to the hospital during the initial months after surgery, and temporary relocation of the family may be necessary. Prolonged periods of stressful hospitalization are likely. A stable social situation is essential for success, and psychosocial evaluation is an important aspect of the pretransplantation process.

KEY POINTS: HEART TRANSPLANT RECIPIENT EVALUATION

- Accurate delineation of the cardiovascular anatomy is required for patients with CHD to plan surgical strategies for harvesting and transplantation.
- Increased PVR is associated with increased mortality after transplantation.
- The PRA test reflects a patient's potential for sensitization to donor HLAs.
- PRA >10% increases the risk of graft loss and is present in about 27% of pediatric recipients.

UNOS waitlist status and mortality

Organ transplantation in the United States is sanctioned by congressional mandate through the National Organ Transplant Act (NOTA). An Organ Procurement and Transplant Network (OPTN) was created and is administered by the UNOS. UNOS has three recipient status categories for patients listed for heart transplantation: status IA, status IB, and status II, with status IA indicating the sickest patients who are in urgent need of transplantation for survival. Status seven patients are those previously listed as status IA, status IB, or status II, but considered temporarily unsuitable to receive a heart transplant, e.g. due to active infection.

Current waitlist mortality ranges from 17 to 30% depending on country and institution. Waitlist mortality also varies with transplant center volume, with a reported 5% mortality in large volume centers compared to 30% in small volume centers [35]. Waitlist mortality is also influenced by patient factors such as age, CHD, weight <3 kg, status 1A, the need for ECMO, and renal dialysis [36, 37]. Increased adoption of VADs and improved pretransplant recipient support has helped to decrease waitlist mortality over time [38].

Recipient pretransplant management

The median waiting period from heart transplant listing to actual surgery currently varies between 60 and 80 days, depending on the child's age, blood group, and list status [39].

Aggressive medical management to achieve stabilization is required and includes supplemental oxygen, diuretics, inotropic support (e.g., dobutamine, dopamine, phosphodiesterase inhibitors), antiarrhythmia therapy, and mechanical ventilation. Children with chronic heart failure often receive digoxin, diuretics including spironolactone, angiotensin-converting enzyme inhibitors, and β-blockade therapy (e.g., metoprolol, carvedilol). Patients with severe LV dilation may need anticoagulation, usually coumadin or heparin, to prevent the development of intracardiac thrombi and systemic embolization. Amiodarone is often chosen for treating arrhythmia. Implantable transvenous defibrillators and, more recently, transcutaneous defibrillators have been effective in pediatric patients large enough for these devices. For patients unsuitable for implantable defibrillators either due to patient anatomy or physiology, Life Vest® (Zoll Medical Corp., Pittsburgh, PA, USA) wearable external cardioverter-defibrillator (ICD) therapy can be a short-term option to enable home discharge while waiting for transplant. Biventricular pacing is an emerging modality to improve myocardial function.

Patients with refractory myocardial failure require mechanical circulatory support as a bridge to cardiac transplantation. Approximately one-third of patients with LVADs have right ventricular dysfunction. Medical support and protection of the right ventricle should be considered during anesthesia induction, maintenance, and surgical dissection. Perioperative management algorithms for VAD-supported patients are delineated in a recent comprehensive review [40]. Extracorporeal life support and other mechanical devices as a bridge to transplant are discussed in Chapters 36 and 37.

Pediatric transplant centers are developing pretransplant management strategies that target modifiable risk factors to reduce post-transplant morbidity and mortality [41]. For example, at Stanford Children's Hospital, identification of perioperative acute kidney injury (AKI) as a risk factor for post-transplant morbidity and mortality especially in the CHD population led to the development of a perioperative renal-protective protocol.

Donor management

In the United States and many other countries, solid organs can be obtained for transplantation by donation after brain death (DBD) or by donation after cardiac death (DCD) [42]. DBD criteria were first established in 1968; prior to this, organs were obtained from DCD, including the first heart transplant. Although DBD soon became the standard for organ procurement, scarcity of available organs led to a reexamination of DCD. During DCD, the goal is to initiate organ procurement as soon as possible after ensuring that death from cardiorespiratory arrest has truly occurred, because viability of the donor organ becomes compromised when the warm ischemic time is prolonged. A North American multidisciplinary panel recently concluded that "Death can be declared after the cessation of circulation and respiratory function for 2 minutes" [43]. Despite DCD being legal and with recipient outcomes that are favorable, ethical issues still surround DCD, and DBD currently remains the primary source of organs [44].

The age distribution of pediatric heart donors is similar to that of heart recipients [3]. Echocardiography is useful for assessment of donor heart function. Widespread malignancy or infection in the prospective donor is an exclusion criterion, but cardiac resuscitation and chest trauma are not contraindications, provided the donor's hemodynamics have been stabilized and inotropic agents are no longer needed or are at minimal doses. Assessing potential donor organs involves evaluating immunocompatability, donor risk factors, travel time, recipient pulmonary hypertension, and donor–recipient size match. In contrast to adult heart transplant, sex mismatch has not been found to significantly affect outcomes [45]. Attempts to limit donor heart ischemia time are important but may be hampered by transport issues.

Donor (allograft) ischemic time is defined as time between donor aortic cross-clamp during organ procurement surgery and donor coronary artery reperfusion during heart transplant surgery [46]. The median donor ischemic time for the current era is 3.5–3.7 hours [46]. Donor ischemic time >4 hours is associated with increased 30-day, 1-year, and 5-year mortality [3, 46]. Conversely, donor ischemic time has not been shown to be associated with major post-transplant morbidity such as CAV or renal dysfunction. Some centers may opt to accept longer donor ischemic times for patients with a high risk of waitlist mortality. At Stanford children's Hospital, our standard strategy is to reperfuse the donor heart for a minimum of one-third the ischemic time prior to cardiopulmonary bypass (CPB) separation.

The anesthetic management of a pediatric organ donor is beyond the scope of this chapter [47, 48].

Developments in donor–recipient size matching

Donor–recipient size matching has important consequences for both organ allocation and post-transplant outcomes for pediatric heart transplantation. Undersized cardiac allografts have the risk of not being able to provide sufficient cardiac output (CO), and oversized allografts confer a risk of compressing neighboring structures such as lungs and subsequent physiological effects [49]. Recent publications have also questioned the approach of using oversized donors for patients with pulmonary hypertension [50]. Approximately 20% of potential pediatric donor allografts without marginal/high-risk characteristics are not used [51]. Innovative techniques to improve donor organ utilization have the potential to reduce pediatric waitlist mortality. Historically, standard clinical practice has been to use donor–recipient body weight ratio (DRBW) and donor–recipient height ratios for allograft size matching. At the time of listing transplant, institutions will define a lower and upper weight limits that they are willing to accept for their patient. A typical range would be 80–160% of recipient body weight. Estimating size match eligibility using traditional measurements such as weight and height assumes a predictable correlation with total cardiac volume. Total cardiac volume, however, may not always correlate with somatic growth. For example, children with advanced heart failure may have a lower than predicted body weight because of failure to thrive or a higher body weight due to fluid overload. Body weight is also an inaccurate correlate of heart size in patients with CHD or RCM where the heart size is often smaller and in patients

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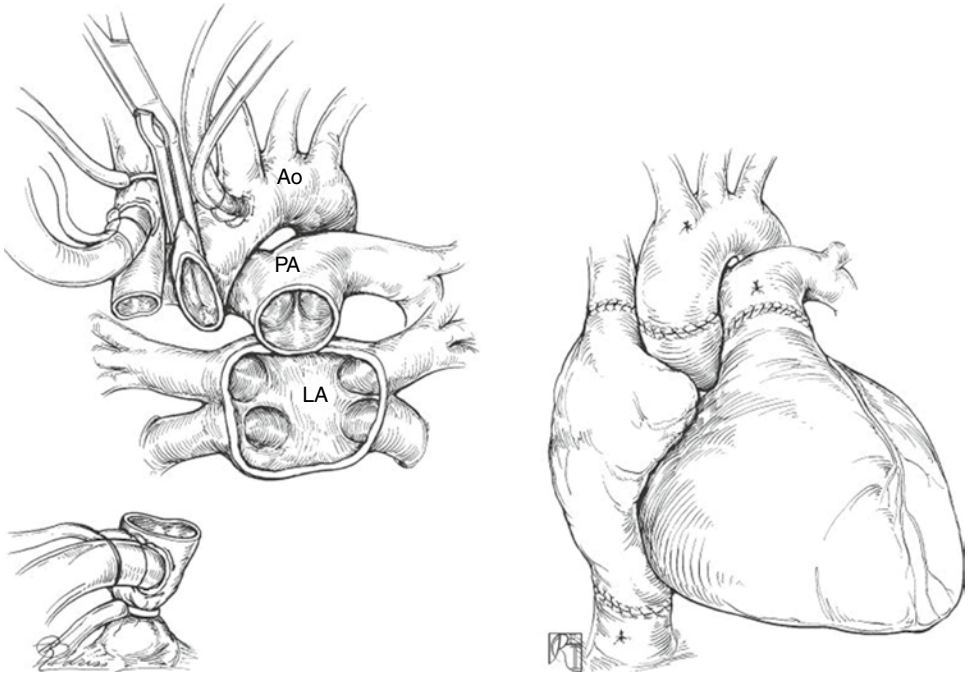


Figure 32.5 "Bicaval" cardiac transplantation. (A) The recipient cardiactomy has been completed. Note the entire recipient right atrium has been removed. (B) The completed implant. The sequence of anastomoses is (i) left atrial, (ii) aortic (cross-clamp removed and heart perfused), (iii) inferior vena cava, (iv) pulmonary artery, and (v) superior vena cava. (Source: Backer et al [56]. Reproduced with permission of Taylor & Francis.)

with dilated cardiomyopathies and cardiomegaly. Heart size matching based on weight also does not account for the complexities of implantation in patients with heterotaxy and cardiac malposition. Waitlist mortality and allograft shortages have led clinical transplant programs to widen their acceptable DRBW to increase the donor pool. Innovative approaches to performing virtual heart transplant fit assessments include using allograft total cardiac volume prediction models and advanced donor imaging such as CT and MRI for a direct virtual transplant assessment [52–54]. Adoption, development, and standardization of these alternative approaches may improve organ utilization.

Surgical technique

Orthotopic heart transplants whereby the recipient heart is excised and replaced in the correct anatomical position by the donor heart is the standard surgical approach. The biatrial anastomoses originally described by Lower and Shumway [55] has now been abandoned in most centers and replaced by the bicaval left atrial cuff technique – the current standard approach for pediatric heart transplant. A small cuff of recipient left atrial tissue is left in place, incorporating all pulmonary veins, and the entire right atrium of the recipient is removed. Standard implantation of the donor heart involves five anastomoses – left atrial cuff, aorta, inferior vena cava (IVC), superior vena cava (SVC) (bicaval anastomoses), and main PA. Surgeons will vary with regard to the order of anastomoses. Two golden rules that apply for all implantations are that the left atrial anastomosis is performed first, and once the left atrial anastomoses and aortic anastomoses are completed, the aortic cross-clamp can be removed and donor heart reperfusion commenced (Figure 32.5) [57]. A meta-analysis found superiority of the bicaval technique in comparison with the biatrial procedure for early atrial pressure, perioperative mortality, tricuspid valve regurgitation, and sinus rhythm [58], although others found no difference in long-term survival [59].

Cardiac transplantation for children with CHD can involve more complex anastomoses and vascular reconstruction such as branch PA reconstruction and aortic arch reconstructions for recipients with palliated single ventricle physiology. Deep hypothermic circulatory arrest may be employed in patients requiring extensive vascular reconstruction.

Anesthetic management

Pre-CPB period

Multidisciplinary preoperative huddle and planning

Children listed for heart transplantation have limited physiological reserves. Even minor changes induced by anesthesia, and surgery can trigger cardiovascular instability and decompensation. Prior to surgery, young infants and children with decompensated heart failure may already be in intensive care with invasive lines and inotropic and respiratory support. More stable patients may be admitted from home at the time of donor acceptance and could have eaten recently. Several hours usually elapse before surgery, but therapy to modify gastric pH and volume and the application of continuous cricoid pressure during induction might be required. Up to 30% of pediatric heart transplants are bridged with a VAD and may be either inpatient or

outpatient and will be on some form of anticoagulation and antiplatelet therapy [60]. Communication between the transplant surgeons, anesthesiologists, operating room staff, and donor procurement team is vital to coordinating care and ensuring allograft ischemia time is minimized. At Stanford Children's Hospital, we hold a preoperative "huddle" attended by the heart failure and transplant teams, intensive care team, the surgeon, anesthesiologists, and perfusionists. At this meeting, donor- and recipient-specific issues are addressed, including allosensitization and plasmapheresis, vascular access, invasive monitoring lines, emergency cannulation techniques, immunosuppressants, including steroids, and the need for urgent reversal of anticoagulation such as warfarin reversal with a prothrombin complex concentrate [60]. We also discuss renal risk stratification and employ renal-protective strategies for patients with a moderate-high risk of postoperative AKI. Stanford Children's renal-protective protocols involve risk stratification of patients for risk of AKI, maintaining adequate renal perfusion through blood pressure management, fluid management, and reducing central venous congestion, pharmacoprophylaxis with pre-, intra-, and postoperative aminophylline and a modified induction protocol to avoid highly nephrotoxic medications in the immediate postoperative period. As part of the huddle, we discuss a patient-specific "flight plan," which addresses all relevant patient specific perioperative issues and is documented in the electronic medical record (Figure 32.6).

Anesthesia induction and monitoring

Premedication and the method of anesthesia induction depend upon the patient's age, cardiac lesion, and cardiopulmonary function. Establishing invasive hemodynamic monitoring prior to induction of anesthesia may not always be feasible and so it is imperative to institute noninvasive patient monitoring prior to the administration of medications that alter hemodynamic and/or respiratory function. Focused transthoracic echocardiography (TTE) may have a role in patients where preinduction arterial lines may not be an option. Qualitative assessment of cardiac function in patients with severely reduced function and septal configuration in patients with pulmonary hypertension can be monitored with a parasternal short-axis view. Anesthesia- or surgery-induced changes in heart rate (HR), preload, afterload, or contractility can precipitate hemodynamic decompensation. Meticulous airway management is vital as hypoxia and hypercarbia aggravate PVR and can further depress CO and high intrathoracic pressures may trigger right ventricular decompensation. Rapid sequence induction may be poorly tolerated in patients with minimal cardiorespiratory reserve. Significant ascites in patients with hepatic dysfunction (e.g. failing Fontan) may necessitate controlled peritoneal drainage peri-induction. A wide variety of anesthetic agents have been used successfully. The desirable and detrimental cardiovascular effects of anesthetic agents are reviewed in Chapter 10. In children with CHD, a fentanyl/midazolam/muscle relaxant anesthetic technique was reported to preserve cardiac index better than volatile agents, provided HR was maintained [61]. Etomidate has minimal effect on hemodynamics and is a useful induction agent in patients with limited cardiovascular reserve. Propofol decreases systemic vascular resistance and reduces preload to the heart, and a bolus should be used with caution if at all. Nitrous oxide has myocardial depressant and pulmonary vasoconstrictor properties and is best avoided. Ketamine supports the circulation by indirectly stimulating catecholamine release. This may be blunted in children with DCM and impaired β-agonist responses, or in patients who are on chronic infusions of β-adrenergic agonists. When the patient's endogenous catecholamine stores are depleted, the drug's direct myocardial depressant effects may then predominate. Regardless of the agent used, hypotension must be anticipated and treated promptly to preserve coronary perfusion. Commencing a low-dose inotrope infusion (e.g. epinephrine 0.01–0.03 mcg/kg/min) prior to induction of general anesthesia provided there are no significant arrhythmias may help avoid hypotension and preserve coronary perfusion. Recent excellent reviews describe the anesthetic management of children in the operating room [62, 63]. A trigger-free anesthetic should be considered for patients with neuromuscular disease such as Duchenne or Becker muscular dystrophy to reduce the risk of malignant hyperthermia like symptoms or anesthesia-induced rhabdomyolysis.

Monitoring during transplantation surgery does not differ from that used for pediatric open-heart surgery. Large-bore vascular access and a rapid infuser device should be available for patients undergoing repeat sternotomy and those on preoperative mechanical circulatory support. Patients with pacemakers or ICDs should have their devices reprogrammed prior to the use of surgical diathermy. TEE is useful for evaluation of intracardiac air, transplanted heart anatomy and function, vascular anastomoses, mural thrombus, and early post-transplant cardiac function. When PA pressure monitoring is indicated, some institutions prefer to place a catheter directly into the PA rather than use a percutaneous balloon-tipped PA catheter. Due to the increased risk of perioperative bleeding in patients with CHD, repeat sternotomy and those on mechanical circulatory support prophylactic anti-fibrinolytics are a useful adjunct.

CPB period

The management on CPB is similar to that in children undergoing cardiac surgery. Ultrafiltration during CPB may benefit the patient by removing excess free water, hemoconcentrating red cells and coagulation factors, and modulating the inflammatory response. Variations in ultrafiltration techniques are institution dependent.

Post-CPB period

Issues of concern include denervated donor heart, global ischemia–reperfusion injury, elevated PVR, right ventricular dysfunction, arrhythmia, hemostasis, and hyperacute rejection.

The transplanted heart is functionally denervated and may have an abnormal response to sympathetic stimulation. Resting HR may be higher than normal because of absent vagal tone. The normal beat-to-beat variations in response to respiration are lost, as are the normal responses of the heart to alterations in body position and carotid body massage. The donor heart cannot abruptly increase HR and CO in

Transplant Flight Plan

Name:
MRN:
DOB:
Date of Listing:
Flight Plan Current as of:

SECTION A: Care Team

Primary Heart failure Cardiologist:
Primary Community Cardiologist:

SECTION B: Risk Assessment

Please identify the degree of estimated risk for each of the following:

AKI: Average - Baseline Creatinine 0.15-0.2
Bleeding: High - Chronic anticoagulation for VAD with aspirin, Plavix and lovenox
Infection: High - Concern for chronic VAD and abdominal infection, on meropenem
Liver Dysfunction: Average - Baseline bilirubin normal at 0.5
Clinically meaningful PH: Average - None, last cath PVR 3.4
Malnutrition: Average - On continuous NJ feeds
Ongoing PLE: Not Applicable

SECTION C: Diagnosis/Physiology/ Anatomy

Current Anatomy: 3-year-old F with DCM s/p Berlin BIVAD (Berlin LVAD, Berlin RVAD).

Most recent catheterization date:
Most recent catheterization data: RA 12, RV 39/14, PA 38/20/29, PCWP 20. CI 3L/min/m2, PVRi 3.4 iWU, SVRi 17.1 WU

SECTION D: LINE MANAGEMENT

Last vascular surveillance:
UE and LE US with Doppler: No thrombus demonstrated. Patent central upper and lower arterial and venous vasculature.
CT Chest/Abd/Pelvis: Thoracic and abdominal aorta is normal in caliber. No evidence of stenosis or aneurysmal dilation.
The following vessels are known to be open: RIJV, RSCV, LIJ, LSCV, RFV, RFA, LFV, and LFA
intravenous/intracardiac Lines Requested During Surgery (in addition to standard CVL, arterial lines, and PIVs: RA and LA.

SECTION E: AKI Prevention Plan

Plan to follow renal protective protocal? yes
Intraoperative Aminophylline: yes
Timing of Aminophylline Administration: Pre-op
Maintain arterial blood pressures around 75th percentile for age? yes
Goal CVP less than 10? yes
Avoid NINJA (nephrotoxic) medications if possible? yes
Intraoperative PD Catheter to be placed during surgery? no
Post-Operative Renal Surveillance Plan (urine collection, biomarkers, etc.): Standard Care

SECTION F: Immunosuppression Plan

Induction: Standard (sensitized)
Plasmapheresis going on to bypass
ATG: yes
Dose/Schedule: 1.5 mg/kg/dose
Total # of Doses: 5 doses over 7 days
Target CD3 Count: < 50

IVIG: yes
Time IVIG to be started: In OR

Maintenance Therapy:

Calcineurin Inhibitor: yes
Drug: Tacrolimus
Anticipated day of initiation: after renal recovery
Anticipated target trough: 10-12

Mycophenolate Mofetil: yes
Anticipated day of initiation: POD #0 per protocol
Anticipated target trough: Not Applicable

Corticosteroid:yes
Anticipated day of initiation: POD #0 per protocol
Anticipated starting dose/schedule: Per Protocol
Anticipated duration of therapy: Not Yet Determined

Surveillance: First biopsy anticipated: Two Weeks

SECTION G: Infectious disease

Recipient CMV status: Pos per transplant, per charting PCR negative, repeat pending
Donor CMV Status: Neg
Recipient EBV Status: Pos
Donor EBV Status: Pos
Other infectious disease issues that need to be addressed: Concern for chronic VAD/abdominal infection, on meropenem. Recommend continuing meropenem post-op.

SECTION H: Pulmonary Vasodilators

Current Pulmonary Vasodilator Therapies: none

SECTION I: Ongoing Management of PLE

Has PLE diagnosis? no

SECTION J: Arrhythmia Management

Has clinically important arrhythmia history? yes
Describe: History of NSVT, EAT, frequent PVCs, ventricular couplets/triplets. Off aminodarone since ..... On Coreg 2 mg BID.
Has pacemaker or ICD that needs to be turned off at the time of surgery? no

SECTION K: Research Protocols

Please describe any research protocols that need to be incorporated into plan, including blood and/or tissue sampling, interventions, and medications: N/A

Figure 32.6 Example of Stanford Children's Hospital pediatric cardiac transplant flight plan. MRN, medical record number; DOB, date of birth; VAD, ventricular assist device; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; NJ, nasojejunal; PLE, protein-losing enteropathy; F, female; DCM, dilated cardiomyopathy; BIVAD, biventricular assist device; RVAD, right ventricular assist device; LVAD, left ventricular assist device; RA, right atrial pressure; RV, right ventricular pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVRi, PVR indexed to body mass index; SVRi, systemic vascular resistance indexed to body mass index; WU, Woods Units, UE, upper extremity; LE lower extremity; US, ultrasound; CT, computed tomography; Abd, abdomen; RIJV, right internal jugular vein; RSCV, right subclavian vein; LIJ, left internal jugular vein; LSCV, left subclavian vein; RFV, right femoral vein; RFA, right femoral artery; LFV, left femoral vein; LFA, left femoral artery; CVL, central venous line; PIV, peripheral intravenous line; RA, right atrial; LA left atrial; AKI, acute kidney injury; CVP, central venous pressure; NINJA, nephrotoxic injury negated by just-in-time action; PD, peritoneal dialysis; ATG, antithymocyte globulin; CD3, CD3 T cells; IVIG, intravenous immunoglobulin; CMV, cytomegalovirus; PCR, polymerase chain reaction; EBV, Epstein–Barr virus; NSVT, nonsustained ventricular tachycardia; EAT, ectopic atrial tachycardia; PVC, premature ventricular contractions; Coreg; carvedilol; ICD, implantable cardioverter-defibrillator.

response to stress because the baroreceptor reflex is disrupted, and patients are dependent on circulating catecholamines. With the loss of the baroreceptor reflex, the patient with the denervated heart may initially show an exaggerated response to hypovolemia with a marked decrease in mean blood pressure and then a delayed exaggerated hypertensive and tachycardia response, due to endogenous catecholamine release. The Frank–Starling (pressure–volume) relationship remains intact and compensates for hypovolemia and hypotension by increasing stroke volume secondary to an increased venous return. Therefore, it is important to maintain adequate preload, especially if vasodilators are administered. Innervation of the peripheral vasculature is preserved, and changes in peripheral vascular resistance may still occur in response to alterations in sympathetic outflow from the vasomotor center due to signals from stretch receptors in the great vessels.

Drugs such as atropine, glycopyrrolate, neostigmine, and pancuronium that act on the heart through vagal or sympathetic neuromechanisms usually will not affect HR. However, there are case reports of profound bradycardia and hypotension following glycopyrrolate–neostigmine administration [64, 65]. α- and β-Adrenergic receptors remain intact, and inotropes such as epinephrine and isoproterenol will cause appropriate responses from the heart.

The donor organ is subjected to ischemia–reperfusion injury, and patients usually require inotropic support for separation from CPB. LV diastolic dysfunction is common and characterized by a restrictive ventricular filling pattern, with a reduced preload reserve and a relatively fixed stroke volume. Sinoatrial node dysfunction is relatively common. Dopamine, epinephrine, or isoproterenol is often selected, and epicardial temporary pacing can be instituted if necessary to achieve the desired HR. Arrhythmias are quite common in the early postoperative period, usually premature atrial or premature ventricular contractions. Compression of intrathoracic structures may be problematic during closure of sternotomy, particularly if the donor heart is relatively oversized [66].

It is important to preserve donor right ventricular function by keeping PVR low normal. Catecholamine release is reduced by ensuring the patient remains adequately anesthetized. Ventilation is facilitated by muscle relaxants, and normocarbia is maintained. Elevations in central venous pressure with low or normal left atrial pressure and reduced mean arterial pressure might be related to right ventricular failure. Elevated PA pressures can be detected by echocardiography and measured invasively. Additional measures to control PVR may be necessary, including pulmonary vasodilator therapy such as NO [67], prostacyclin, phosphodiesterase inhibitors, and isoproterenol. At Stanford Children's Hospital, we routinely separate from CPB with inhaled nitric oxide (iNO) 20 ppm, dopamine, epinephrine, and milrinone infusions following pediatric heart transplants.

More extreme hypocapnia may help, but also causes cerebral vasoconstriction and leftward shift of the oxygen dissociation curve. Cerebral oximetry monitoring using near-infrared spectroscopy is helpful. If the patient's CO remains inadequate despite maximal drug therapy, mechanical right ventricular assist or ECMO may be employed [68].

Blood loss during heart transplantation can be considerable and is associated with increased morbidity and mortality. Blood products are cytomegalovirus-matched, leukoreduced, and irradiated, but coagulation management is no different from that for other open-heart surgeries in children (see Chapter 16). For infants, some centers wash packed red blood cells to reduce the potassium load. Citrate-induced hypocalcemia impairs contractility and coagulation; this may be minimized by initiating a calcium infusion (calcium chloride 10–30 mg/kg/hour). Rapid platelet transfusion may aggravate PVR. Patients on preoperative mechanical circulatory support often have an acquired von Willebrand deficiency, and cryoprecipitate can be a useful adjunct to help achieve hemostasis [69]. A multimodal approach to hemostasis management should be employed and there is an increasing trend for centers to use prothrombin complex concentrates to achieve perioperative hemostasis [60, 70].

Intraoperative immunosuppression regimens are institution specific. At Stanford, this is discussed during the preprocedural huddle and the medications are ordered by the transplant team to arrive in the operating room with the patient.

KEY POINTS: HEART TRANSPLANT: PERIOPERATIVE MANAGEMENT

- Patients with end-stage heart failure often require anticoagulants and antiarrhythmia therapy.
- Satisfactory transplantation outcomes require excellent communication and collaboration between the multiple disciplines involved in perioperative care.
- Many transplant candidates have minimal cardiopulmonary reserve and may decompensate during anesthesia induction.
  - 17–30% of listed children die while waiting for a donor heart, with infants having the highest waitlist mortality.
  - Increased use of VADs has helped to reduce waitlist mortality.
  - Failing Fontans are an increasing cohort of pediatric heart transplants.
- Postoperative morbidity is directly related to the number of blood products transfused.

Failing Fontan transplants

In North America, a growing cohort of pediatric heart transplants are for failing single ventricle palliation. Failing single ventricle physiology accounted for 36% of CHD transplants in the early era (1990–2002) compared to 67% in the more recent era (2006–2017) [11, 12]. Most of the single ventricle transplants are for failing Fontans, followed by the failing Glenn stage [71]. Transplantation after stage 1 palliation is relatively uncommon [71].

Failing Fontan patients may be listed for heart transplant for several different reasons, including ventricular systolic or diastolic dysfunction, atrioventricular valve regurgitation, atrial or ventricular arrhythmias, high Fontan pressures and venous congestion, lymphatic failure such as plastic bronchitis or protein-losing enteropathy (PLE), and hepatic or renal

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dysfunction. Because of this heterogeneous and often-slowly progressive nature of Fontan failure, there are no clear consensus guidelines for optimal timing for heart transplant listing. Fontan heart transplants represent a high-risk cohort with increased CPB times, increased donor ischemic times, and increased bleeding risk [71, 72]. Early era multicenter registry studies and single-center studies reported that Fontan patients had decreased early survival after heart transplant when compared with other forms of CHD and cardiomyopathies. In the current era, expected survival after heart transplant for Fontan patients is comparable to other CHD patients [41]. This is a reflection in improved overall survival for pediatric heart transplantation despite increased case complexity [15, 71]. Improvements in perioperative care, recognition, and mitigation of modifiable risk factors have helped with improved outcomes. Institutions have developed their own multifaceted approach to deal with issues specific to this population [41]. Issues include complex surgical dissection and implantation, longer allograft ischemic times in Fontans (>4 hours), vasoplegia, aggressively treating for and monitoring primary graft failure, AKI, and the impact of PLE [41]. The association between the Fontan circulation and renal dysfunction, driven by renal venous congestion and low CO, has led to increased efforts to target the prevention of perioperative AKI in this population [73]. Data also suggest there may be an opportunity to improve outcomes by optimizing nutrition and reducing malnutrition in Fontan patients [74, 75]. Figure 32.7 illustrates a single-center checklist to guide perioperative management for Fontan heart or CHLTs.

Combined heart and liver transplantation

Pediatric patients with relatively simple cardiac defects can successfully undergo liver transplantation with equivalent outcomes reported for children with and without CHD [76, 77]. The consensus remains that severe cardiac defects should be corrected prior to liver transplantation to avoid unacceptable transplantation mortality. Lesions of concern include significant cardiopulmonary disease, pulmonary hypertension [78], hypoxemia (PaO_2 < 50 mmHg) – either from cardiac shunt or hepatopulmonary syndrome – elevated central venous pressure (>15 mmHg), and low CO. Successful liver transplantation outcome after bidirectional Glenn palliation for HLHS has been reported [79]. Although the first pediatric CHLT was reported in 1984, this remains relatively uncommon in children [80]. UNOS database shows that only 21 out of 387 heart liver transplants reported to date (2021) were in patients under 18 years of age.

Elevated central venous pressure, hepatic congestion, and reduced CO in the Fontan circulation lead to the development of Fontan-associated liver disease (FALD). All patients develop some degree of FALD after a Fontan, but it is unclear which ones will develop clinically significant liver disease. Studies have shown that the severity of FALD-related liver histopathology most strongly correlates with overall time since Fontan completion [81]. Almost 100% of Fontan patients have histological evidence of fibrosis by the time they reach adolescence and 40% develop bridging fibrosis at 10 years post Fontan [81]. FALD ranges from bridging liver fibrosis to cirrhosis, portal hypertension, and, rarely, hepatocellular carcinoma [82]. Variceal-related gastrointestinal bleeding and liver synthetic function derangements remain uncommon. Improved awareness and surveillance for FALD have led to an increasing number of patients being listed for CHLT. Currently, there are no consensus guidelines for diagnosing and monitoring FALD and which patients to list for heart–liver versus heart transplant. A recent study suggested that cirrhosis on imaging should prompt consideration for CHLT rather than heart transplant alone [82]. A multidisciplinary group recently proposed an algorithm of who to list for heart transplant versus heart–liver transplant (Figure 32.8). Some centers have adopted surveillance cardiac catheterization combined with transjugular liver biopsy in all patients 10–15 years after Fontan completion. Liver fibrosis seen in these patients are heterogeneous and, therefore, biopsy sampling error may underestimate the degree of liver involvement. Despite the difficulties with deciding who to list for heart–liver transplant, studies have shown that CHLT patients have 1- and 5-year survival rates similar to heart transplant alone [70, 83]. Although the etiology is unknown, CHLT patients appear less vulnerable to acute cellular- and antibody-mediated rejection (AMR) [83]. The adult transplant literature indicates that CHLT attenuates cardiac allograft vasculopathy by decreasing the rate of plaque volume and plaque index progression, thereby providing better coronary-related clinical outcomes [84]. A recent single-center study of pediatric and young adult Fontan recipients also reported comparable post-transplant outcomes in patients receiving heart–liver transplants and heart transplant alone despite higher inotropic requirements and more advanced liver disease in the heart–liver cohort [82].

Stanford University investigators have published reports of up to nine pediatric heart–liver transplants for failed single ventricle palliation where the organs were procured and implanted en bloc [70, 82]. An advantage of the "en bloc" technique when the heart and liver are implanted together during CPB is that the new heart is protected from the hemodynamic and metabolic derangements that are typically seen when the liver is implanted and reperfused separately after CPB separation.

Reliable estimation of perioperative mortality is challenging and requires separate consideration of the risks posed by hepatic and cardiac dysfunction. Important challenges include the intraoperative management of massive transfusion and vasoplegia [70, 82] and postoperative renal dysfunction [82, 84, 85].

Overall risk and transplant listing for CHLTs is influenced more by cardiac status than liver status [86]. Current UNOS policy allows patients waitlisted for heart–liver to be also waitlisted for heart-only and liver-only transplantation. If a heart–liver patient is offered a heart or a liver, the additional organ from the same donor is also allocated.

Heart–lung transplantation

HLT is covered in detail later in this chapter. Briefly, institutional preferences drive HLT versus single- or double-lung transplant in patients with elevated PVR. Current ISHLT data show comparable outcomes for HLT versus lung transplant or double-lung transplant for patients with idiopathic pulmonary arterial hypertension [87]. Disadvantages of HLT include significantly

Perioperative Checklist for Fontan Heart and Heart-Liver Transplants

Preoperative huddle discussion topics

Vascular access-Check recent vascular map (CT/US) to confirm patency of vessels.

Difficulty of re-opening & rescue strategy-right neck vs right groin.

Significant collaterals (Aorto-Pulmonary or Veno-Venous): bleeding risk during re-opening.

Significant Aorto-Pulmonary (AP) collaterals: run higher flows on CPB & maintain higher MAPS to preserve end organs e.g., kidneys/liver.

Baseline renal function & renal protective strategies: Peri-op aminophylline & higher intra-op target MAP. Post op HD line: need & timing.

Recent INRs & Coagulation results: Reversal with KCentra (see below) & products during dissection.

Esophageal/gastric varices. Consider pediatric TEE probe if concern for varices.

Significant abdominal ascites: plan for controlled intra-operative drainage.

Octreotide infusion for portal hypertension.

Antibiotics (consider piperacillin/tazobactam for heart-liver patients).

Anesthesia induction/maintenance

Check *insitu* lines e.g. PICC- is it central.

Sedated peripheral arterial line if possible.

If systolic function moderate/severely reduced & no arrythmias consider low dose epinephrine e.g. 0.02-0.03mcg/kg/mn peri-induction.

Patients with diastolic dysfunction/PLE/liver dysfunction often in vasodilated state: consider vasopressin infusion.

Right internal jugular triple lumen line (high approach in neck).

If possible: left femoral arterial line and left femoral venous sheath (surgeons may need right groin for heart-liver cannulation). Venous sheath connected to rapid infuser.

Once donor heart visualized: reversal with KCentra + Vit K if INR > 1.8 & start coagulation products (e.g. platelets) for dissection if needed.

Pre-treatment INR	1.8–<4	4–6	>6
Kcentra dose (units based on Factor IX content)	25 units/kg	35 units/kg	50 units/kg
Maximum dose	Not to exceed 2500	Not to exceed 5000	Not to exceed 5000

Vitamin K Dose 5-10 mg IV. Administering with Vit K will help maintain factor levels

TXA as per intra-operative coagulation pathway.

Cerebral and renal oximetry monitoring.

Octreotide 1-2 mcg/kg/h, max dose 100 mcg/h until shortly after reperfusion-stop after separation from bypass.

Start insulin infusion for blood glucose > 200.

CPB strategy

Consider higher flows to maintain higher MAPS & end organ perfusion especially if AP collateral burden is high.

Ensure adequate venous decompression (brain, liver, & kidneys).

Minimum Hct on CPB: 30%.

Vasoplegia: Consider vasopressin to maintain MAPS.

Refractory vasoplegia (seen more often with Fontan VADS): Consider adding methylene blue (2mg/kg over 30 mins); methylene blue infusion if needed (0.5mg-1.0 mg/kg/hr); Consider switching vasopressin to norepineprhine infusion. Consider hydroxycobalamin 5g over 15 min (obtained from Stanford adult hospital).

Post bypass

Goals: 1. Protect right heart & liver allograft (for heart-liver patients).
2. Be prepared for massive blood product transfusion (especially heart-liver patients).

Dopamine/epinephrine/calcium infusion +/–milrinone (if not vasoplegic).

Consider vasopressin for post-operative vasoplegia.

Nitric oxide 20 ppm; Consider ICU ventilator & in-line suction catheter.

Single digit CVP; Keep a close eye on right heart function by TEE.

Have Feiba available (Recommended dose: 10 units per kg X 2–3).

Fibrinogen concentrate to optimize fibrinogen level (Goal fibrinogen 300).

Platelets (usually minimum 2-4 units). May need more for heart-liver.

Cryoprecipitate (usually 10 pack for heart transplants and 20 pack for herat-liver).

Massive transfusion or keep ahead with PRBC & FFP.

Check Lactates & correct base deficit; Repeat TEG & fibrinogen for refractory bleeding/ongoing coagulopathy.

Immunosuppressants – IVIG (*see IVIG tip sheet*).

Hematocrit Goals per Intraoperative coagulation pathway

Non-neonate: complex 2ventricle repair
Minimum Hct pre-CPB (%): 30
Minimum Hct on CPB (%): 30
Target Hct CPB separation (%): 30–35
Minimum Hct for transfer to ICU (%): 30

Obtain satisfactory hemostasis prior to leaving operating room.

Take spare blood products for transport in case of re-bleeding.

Figure 32.7 Perioperative checklist for Fontan patients undergoing heart or combined heart–liver transplants: Stanford Children's Approach. CT, computed tomography; US, ultrasound; CPB, cardiopulmonary bypass; MAPS, mean arterial pressures; HD, hemodialysis; INR, international normalized ratio; K_{Centra}, prothrombin complex concentrate; TEE, transesophageal echocardiography; PICC, percutaneously inserted central line; PLE, protein-losing enteropathy; TXA, tranexamic acid; VAD, ventricular assist device; PRBC, packed red blood cells; FFP, fresh-frozen plasma; TEG, thromboelastogram; IVIG, intravenous immunoglobulin.

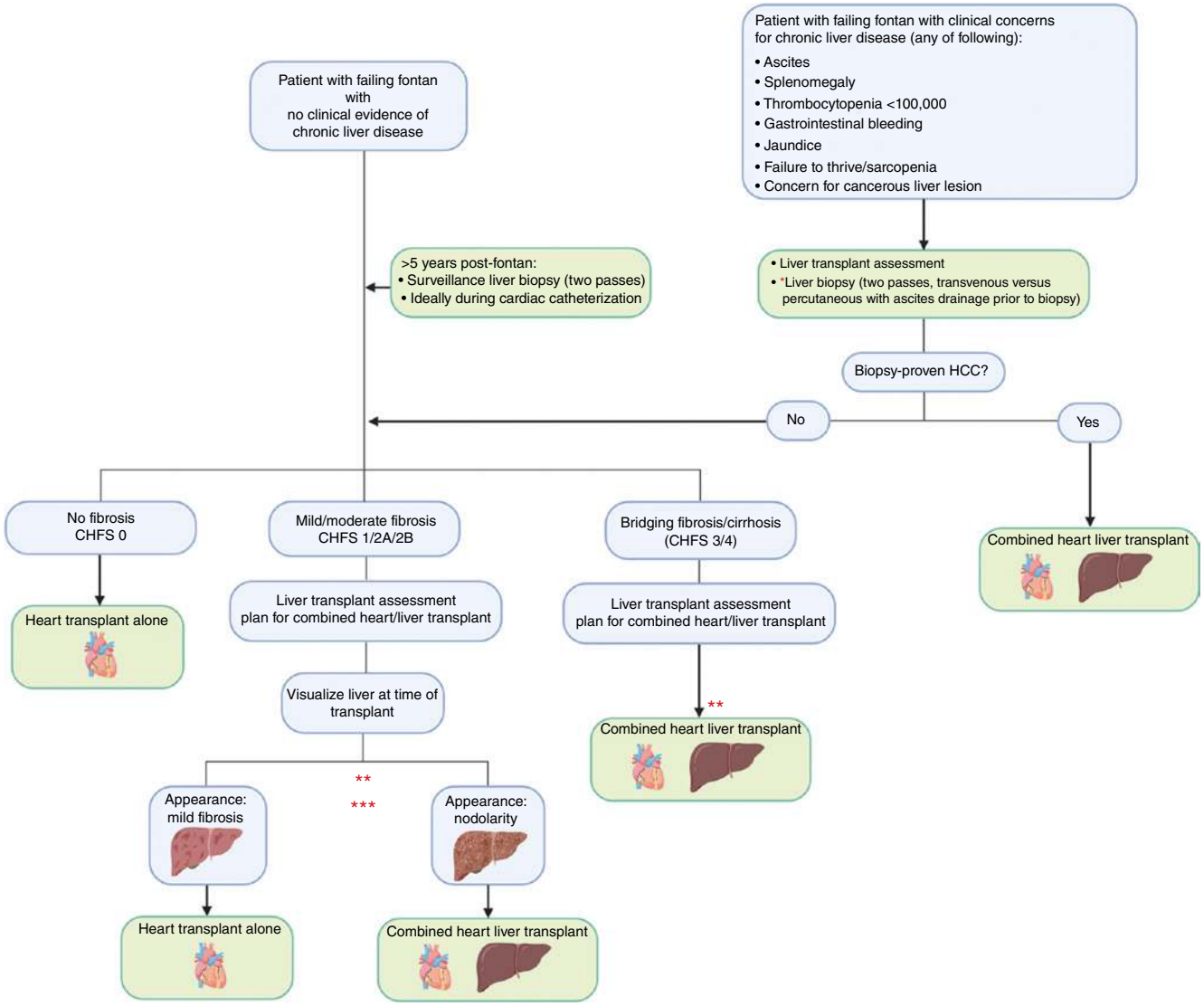


Figure 32.8 Algorithm for heart transplant versus combined heart–liver transplant in patients with Fontan-associated liver disease. (Source: Emamaullee et al. [81]. Reproduced with permission of Wolters Kluwer Health, Inc.)

longer wait times, the need for higher levels of immunosuppression in patients with double-organ transplants, and surveillance of two organs for rejection. Currently, HLT is recommended in patients with demonstrable LV dysfunction and/or in patients with complex CHD with elevated PVR.

Immunosuppression

Immunosuppression following heart transplantation is lifelong. Despite advances in immune therapy, rejection continues to be a major source of morbidity and mortality in the postoperative period. Pediatric heart transplant provides a unique immunological opportunity because the development of the immune system extends beyond infancy into childhood. T-cell responses and phenotype are naive compared with adults, with decreased expression of integrins and adhesion molecules. Younger age at the time of transplantation is associated with better long-term survival and lower frequency of rejection compared with older children [88]. Infants and young children (up to 5 years of age) have undergone transplantation across ABO barriers without developing clinical rejection as discussed earlier.

Choice of immunosuppressives is largely guided by institutional experience and the recipient's clinical profile, rejection history, and comorbid associations. Currently, there are no randomized trials to guide management. Stanford Children's Hospital current immunosuppression protocol is attached as an example (Table 32.4). Typical clinical use of these agents is summarized below [89].

Immunosuppression consists of an induction and maintenance phase with additional therapies to manage rejection.

Induction therapy. Induction phase allows for rapid establishment of immunosuppression. Approximately 75% of transplant recipients between 2010 and 2018 received induction therapy [4]. The most common agent used are polyclonal antilymphocyte or antithymocyte globulin. Despite its popularity in children, significant benefits of induction therapy for survival, CAV, or incidence of rejection are yet to

Table 32.4 Induction and maintenance of immunosuppression following heart transplantation in children: stanford protocol

Induction therapy: Administered in the operating room following hemostasis from CPB.
Methylprednisolone: 10 mg/kg (max. dose is 500 mg).
POD# 0–7: 1. Rabbit antithymocyte globulin 1.5 mg/kg/dose; 5 doses given over 5–7 days.
2. Methylprednisolone: 3.3 mg/kg every 8 hours X3 doses and then tapered to 0.4 mg/kg/dose, twice daily. Once tolerating oral medications prednisone/prednisolone at 0.5 mg/kg, twice daily can be started.
3. Mycophenolate mofetil: 600 mg/kg twice daily.
4. Tacrolimus: 0.05 mg/kg orally started on POD#5 and if renal function is normal.

Maintenance therapy: Patients may be weaned from prednisone based on the following criteria
If first biopsy is negative or on POD #7–14, whichever comes first:
- Did not receive preoperative desensitization therapy pretransplant
- Compatible retrospective crossmatch (regardless of virtual crossmatch results)
- Tacrolimus trough >7 ng/mL
- Ventricular function is normal
- There are no concerning donor-specific antibody.

If above criteria are not met, steroids are continued and weaned gradually over 6 months.
Tacrolimus: Dose is adjusted to achieve target troughs of 10–12 ng/mL for the first 3 months, then 8–10 ng/mL for months 3–6, then 7–10 ng/mL for months 6–12, then 5–8 ng/mL after the first postoperative year. This is continued indefinitely. Dose/target trough may be adjusted in patients receiving PSI medications and/or those with or at risk for chronic kidney disease.
Mycophenolate mofetil: Dose: 600 mg/m^2/dose PO (max. 1,000 mg) twice daily. To be continued indefinitely.

Sensitized protocol
If the patient is being treated under "sensitized" protocol due to the presence of antibodies, additional medications may be necessary during the perioperative and induction phase. Plasmapheresis 1.5 volume exchange during CPB.
Intravenous gammaglobulin after separation from CPB.

be demonstrated in children [4]. Results of a prospective multicenter clinical trial are awaited.

Maintenance therapy. The objective is to prevent acute and chronic rejection while minimizing the adverse effects of immunosuppression. All regimens involve a calcineurin inhibitor. Adjunct therapy may include an antipurine agent or mammalian target of rapamycin (mTOR) inhibitor. Often, corticosteroids are also administered, although many programs attempt to limit or avoid their long-term use. Tacrolimus and MMF or mycophenolic acid (MPA) are the most common agents for maintenance immunosuppression at the time of hospital discharge [4] (Figure 32.9).

Immunosuppressive therapies can be categorized by their actions into seven groups as follows:
1. Broad-spectrum immunosuppressants – corticosteroids
2. Calcineurin inhibitors – cyclosporine and tacrolimus
3. Antiproliferative(purine) agents – MMF and azathioprine
4. Antibodies against interleukin-2 (IL-2) – basiliximab and daclizumab
5. TOR inhibitors – sirolimus
6. Monoclonal and polyclonal T-cell antibodies – anti-CD3 monoclonal antibody (OKT3), antithymocyte globulin (ATG), antilymphocyte globulin
7. Nondrug therapies – total lymphoid irradiation, photopheresis, and plasmapheresis.

Calcineurin inhibitors

Overall survival of transplanted patients increased from 40 to 70% after the introduction of cyclosporine (Sandimmune, Neoral) in 1982. Cyclosporin binds to cyclophilin within the cytoplasm of T cells; this complex inhibits calcineurin phosphatase, thus interfering with the transcription of key cytokines such as IL-2, required for T-cell activation and proliferation. It is not a myelosuprressant and B cells, macrophages and granulocytes are unaffected. Microemulsified formulation of cyclosporin provides better bioavailability and lower rejection rates than the original preparation that had unpredictable absorption. Therapeutic drug monitoring is essential because the therapeutic window is narrow and other drugs influence drug levels. Cyclosporine trough levels are usually maintained in the range of 100–300 ng/mL. Adverse effects may be dose-related and include toxicity of renal, hepatic, and neurological systems, hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia.

Tacrolimus (Prograf, FK506) binds to a different cytosolic-binding protein (FK-binding protein) and has been particularly effective as a rescue treatment in cases where recurrent rejection has occurred with cyclosporine. Overall patient survival does not differ between the two agents, but there appears to be less rejection with tacrolimus and an improved adverse effects profile with respect to hypertension, dyslipidemia, and long-term renal function [4, 90, 91]. Like cyclosporine, the therapeutic window is narrow and blood levels can be affected by other medications. Trough levels are maintained in the range of 5–15 ng/mL. In recent years, cyclosporine and tacrolimus have been used in a similar percentage of patients and MMF has largely replaced azathioprine use early after transplant (Figure 32.9). There is a trend to shift patients who are 5 years post-transplant from cyclosporine-based regimens to tacrolimus-based regimens [4].

Antiproliferative agents

Agents such as azathioprine (Imuran) and MMF (CellCept) inhibit lymphocyte proliferation by interfering with purine synthesis. One of these agents may be added to calcineurin inhibitor therapy. The choice of either MMF or azathioprine did not have an impact on rejection rate within the first year in the pediatric heart transplant population [4].

Azathioprine is a purine antagonist that inhibits T and B cells. Bone marrow depression is common, and dosing is guided by the white blood cell count. Its use has declined considerably in the past decade.

MMF converts to MPA, an inhibitor of purine synthesis. B- and T-cell lymphocytes are suppressed because they lack a salvage pathway. Absorption is variable, and dosing

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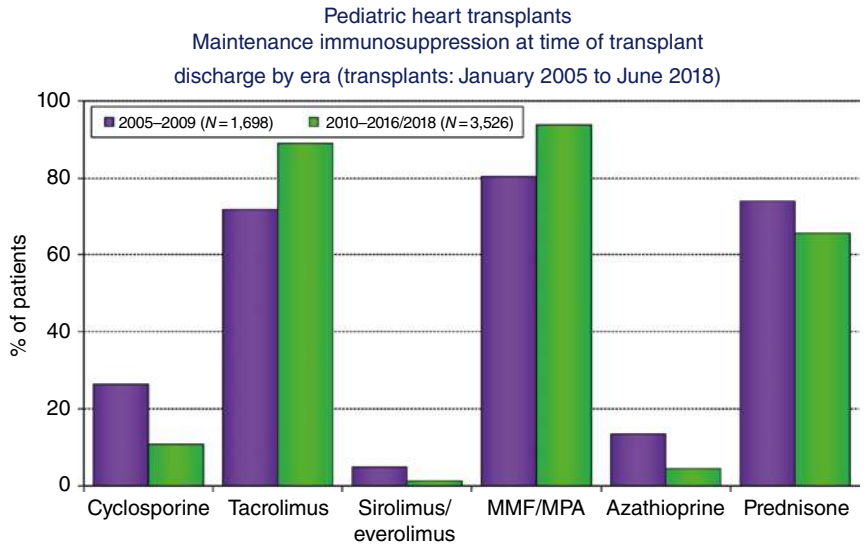


Figure 32.9 Maintenance immunosuppression at the time of hospital discharge following heart transplantation by era (pediatric transplants, January 2005 to June 2018). Analysis is limited to patients who were alive at the time of the discharge. MMF, mycophenolate mofetil; MPA, mycophenolic acid. (Source: Rossano et al. [4]. Reproduced with permission of Elsevier.)

may be guided by blood levels. Gastrointestinal side effects rather than bone marrow depression are the usual dose-limiting factor.

mTOR inhibitors

Proliferation signal or mammalian TOR inhibitors, everolimus and sirolimus (rapamycin), are newer agents that provide attractive options for use in heart transplantation because they are immunosuppressive and antiproliferative, inhibit vascular smooth muscle and myofibroblast proliferation, and can prevent progression of CAV. mTOR inhibitors work synergistically with calcineurin inhibitors and thus permit the minimization of calcineurin inhibitors without compromising efficacy. This approach is advantageous for most heart transplant recipients and might provide particular benefit in specific cases, such as patients with cardiac allograft vasculopathy, malignancies, and renal dysfunction, or in patients intolerant to other immunosuppressive agents. Sirolimus may inhibit the process of CAV. Adverse effects include hyperlipidemia, wound healing complications, and proteinuria [92]. These drugs inhibit wound healing. Patients taking mTOR inhibitors and scheduled for elective surgery must be switched 2–4 weeks preoperatively to other medications and then restarted 2–4 weeks postoperatively.

Corticosteroids

Corticosteroids are nonspecific anti-inflammatory agents widely used in the precyclosporine era. Steroids decrease cytokine production and reduce the circulating CD4+ T cells. Although a mainstay in induction therapy, steroids are currently used in combination with other immunosuppressants early in transplant. Centers try to minimize the dose and taper off by 6 months because of the myriad of side effects including higher infection risk, diabetes mellitus, bone demineralization, and coronary artery disease. Rejection risk may increase when steroids are withdrawn.

Rejection therapy

High-dose corticosteroid, usually methyl prednisolone, is the first-line therapy for acute rejection. Recurrent moderate rejection can usually be controlled with enhanced maintenance therapy (tacrolimus, sirolimus) and corticosteroids. Other agents such as polyclonal anti-T antibodies are reserved for severe rejection that is refractory or causing hemodynamic compromise.

Chronic rejection is manifest as coronary vasculopathy. There are no proven therapies that can halt or reverse this process, and retransplantation is the most suitable option for advanced diffuse disease. It remains controversial whether statins affect the progression of allograft vasculopathy or aid in its prevention in children [93].

KEY POINTS: IMMUNOSUPPRESSION AND REJECTION

- Infants have immature immune systems and appear immune-tolerant, as evidenced by their better long-term survival and the success of ABO-I heart transplantation.
- Although induction therapy is commonly employed, it does not appear to convey any survival advantage in children.
- CAV is the leading cause of death after 1 year of pediatric heart transplant.
  - Recipients in acute rejection represent an extremely high-risk group for general anesthesia and require careful hemodynamic monitoring.

Outcome following heart transplantation

Kaplan–Meier survival curves for patients of differing ages at transplant are shown in Figure 32.10. The youngest recipients have the longest median survival to 24.5 years, although

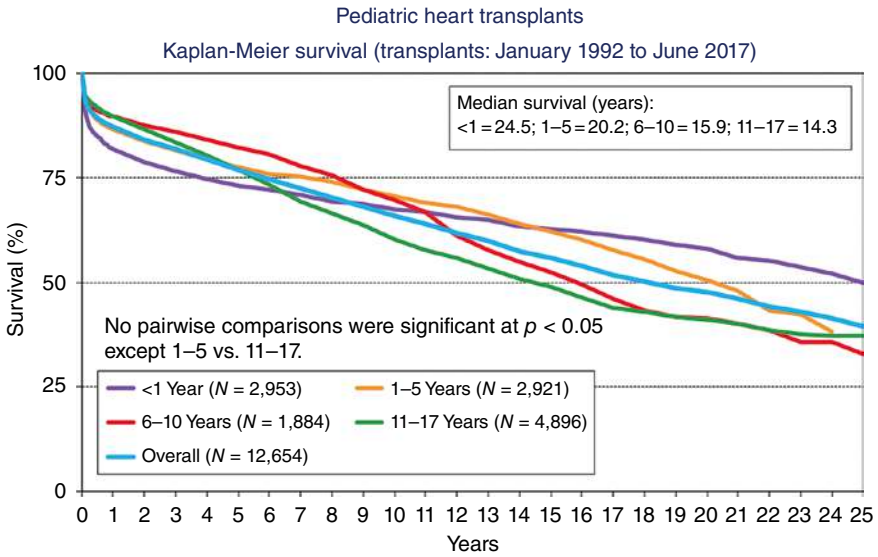


Figure 32.10 Kaplan–Meier survival after heart transplantation (transplants: January 1982 to June 2017). (Source: Rossano et al. [4]. Reproduced with permission of Elsevier.)

Table 32.5 Causes of early and late mortality after pediatric heart transplantation (deaths: January 2005 to June 2018)

Pediatric heart transplants cause of death (deaths: January 2005 to June 2018)						
Cause of death	**0–30 Days (*N* = 280)**	**31 Days to 1 Year (*N* = 347)**	**>1–3 Years (*N* = 283)**	**>3–5 Years (*N* = 235)**	**>5 –10 Years (*N* = 435)**	**>10 Years (*N* = 554)**
Cardiac allograft vasculopathy	3 (1.1%)	9 (2.6%)	37 (13.1%)	39 (16.6%)	90 (20.7%)	127 (22.9%)
Acute rejection	14 (5.0%)	52 (15.0%)	47 (16.6%)	35 (14.9%)	44 (10.1%)	24 (4.3%)
Lymphoma	0	10 (2.9%)	9 (3.2%)	10 (4.3%)	19 (4.4%)	36 (6.5%)
Malignancy, other	0	2 (0.6%)	3 (1.1%)	1 (0.4%)	7 (1.6%)	22 (4.0%)
CMV	0	6 (1.7%)	0	0	0	0
Infection, non-CMV	18 (6.4%)	51 (14.7%)	15 (5.3%)	15 (6.4%)	20 (4.6%)	37 (6.7%)
Graft failure	107 (38.2%)	75 (21.6%)	119 (42.0%)	81 (34.5%)	177 (40.7%)	191 (34.5%)
Technical	23 (8.2%)	2 (0.6%)	0	1 (0.4%)	4 (0.9%)	6 (1.1%)
Other	22 (7.9%)	23 (6.6%)	14 (4.9%)	20 (8.5%)	24 (5.5%)	37 (6.7%)
Multiple organ failure	39 (13.9%)	65 (18.7%)	14 (4.9%)	11 (4.7%)	23 (5.3%)	28 (5.1%)
Renal failure	0	7 (2.0%)	4 (1.4%)	4 (1.7%)	3 (0.7%)	17 (3.1%)
Pulmonary	9 (3.2%)	29 (8.4%)	13 (4.6%)	10 (4.3%)	15 (3.4%)	14 (2.5%)
Cerebrovascular	45 (16.1%)	16 (4.6%)	8 (2.8%)	8 (3.4%)	9 (2.1%)	15 (2.7%)

Source: Data from Rossano et al. [4].
CMV, cytomegalovirus

the attrition rate is highest in the first few months [4]. Recipients who survive to 1-year post-transplant have excellent long-term survival. Table 32.5 lists the causes of early and late (10-year) mortality from ISHLT registry data [4]. ISHLT follow-up data on complications up to 10 years after transplantation are shown in Table 32.6 [94].

Rejection

Rejection is defined by the Pediatric Heart Transplant Study Group as the clinical decision to intensify immunosuppression in association with either histopathology or myocardial dysfunction [95].

The overall incidence of treated rejection in all age groups from hospital discharge to 1-year post-transplant has decreased from 24 in the prior era (2005–2009) to 13% in the most recent era (2010–2018). [4] An episode of treated rejection within 1-year post-transplant is associated with worse survival. The use or type of induction therapy at the time of hospital discharge was not associated with an increased risk of rejection [4]. However, the use of cyclosporine for maintenance therapy at the time of hospital discharge was associated with a higher risk of rejection compared with tacrolimus [4].

Four clinical types of rejection are described (Table 32.7). Hyperacute rejection is rare and manifests soon after

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Table 32.6 Post-heart transplant morbidity. Cumulative prevalence in survivors within 10 years post-transplant (follow-ups: April 1994 to June 2006)

Outcome	Within 10 years (%)
Hypertension	72.3
Renal dysfunction	17.4
Abnormal creatinine <2.5 mg/dL	13.2
Creatinine > 2.5 mg/dL	1.6
Chronic dialysis	1.6
Renal transplant	1.1
Hyperlipidemia	38.2
Diabetes	4.5
Coronary artery vasculopathy	16.7

Source: Data from Boucek et al. [94].

Table 32.7 Characteristics of cardiac rejection

Type of rejection	Mechanism	Approximate onset after transplantation
Hyperacute	Preformed antibodies	Minutes to hours
Acute cellular	T-cell-mediated	Any time (often first 3–6 months)
Acute humoral	Antibodies	Days to weeks
Chronic (coronary artery vasculopathy)	Both humoral and cellular	After the first year

Source: Data from Chan et al. [90].

transplantation. It is mediated by preformed recipient cytotoxic antibodies against donor heart antigens and often leads to intractable heart failure. On average, pediatric heart transplant recipients have two acute rejection episodes during the first 3 years after transplantation, although about one-third remain rejection free. ACR is fatal in <10% of episodes; however, it is the commonest cause of death between 30 days and 3 years after heart transplantation. Acute rejection that occurs more than 2 years after transplantation is linked to poor compliance with therapy and carries a poor long-term prognosis.

Clinical evidence of rejection ranges from no symptoms to tachycardia, tachypnea, lethargy, irritability, poor feeding, fever, hepatomegaly, new murmur, gallop rhythm, and new-onset arrhythmias. Endomyocardial biopsy remains the "gold standard" for the diagnosis of acute allograft rejection. Specimens are graded for rejection based on the numbers of infiltrating lymphocytes and the presence of myocyte injury [96]. Rejection is graded using standardized scales. For ACR, grade 0 R indicates no rejection, grade 1 R mild rejection, grade 2 R moderate rejection, and grade 3 R severe rejection. In the diagnosis and treatment of AMR, ISHLT developed a pathology-based AMR grading system [97].

Endomyocardial biopsy is expensive, invasive, technically challenging in small children, and carries some risks of cardiac perforation and tricuspid valve damage in addition to the need for anesthesia and sedation. Further, "biopsy-negative" acute graft dysfunction can occur. Noninvasive surveillance such as circulating donor-derived cell-free DNA is being considered [98]. The use of echocardiography as a noninvasive method of diagnosing acute rejection is unresolved. Indices of systolic and diastolic dysfunction are reportedly useful but have disadvantages [99–101]. However as of now, there are no noninvasive surveillance techniques that consistently or accurately diagnose or predict rejection.

Surveillance for late rejection is controversial, and experience in children is limited. Our institution performs annual cardiac catheterization, biopsy, and coronary angiography. In adults, intravascular ultrasound findings at 1 year are a powerful predictor of subsequent mortality, nonfatal cardiac events, and the development of angiographic coronary disease.

Treatment of rejection

Treatment depends on several patient factors such as time after transplant, type of rejection, presence of symptoms, infection, hemodynamic changes, and compliance with medications. While mild rejection may not require any acute changes to therapy, moderate or severe rejection will require treatment and/or hospital admission.

High-dose corticosteroid, usually methylprednisolone, is the first-line therapy for acute rejection. Recurrent moderate rejection can usually be controlled with enhanced maintenance therapy (tacrolimus, sirolimus) and corticosteroids. Other agents such as polyclonal anti-T antibodies are reserved for severe rejection that is refractory or causing hemodynamic compromise.

Coronary allograft vasculopathy

CAV and primary graft dysfunction (PGD) are the two leading causes of mid- and late-term mortality after pediatric heart transplant [101]. CAV accounts for >25% of late deaths and is the most common indication for retransplantation [16, 18]. A recent multicenter study demonstrated freedom from CAV at 10 years post-transplant of 77%. [102]. However, by 15 years post-transplant, almost 50% of all transplant recipients have developed CAV [4]. CAV is a diffuse disease characterized by concentric smooth muscle and intimal hyperplasia that begin in the distal, small vessels and progress to involve the intramyocardial and epicardial arteries. It is not only immune mediated but also influenced by non-immune risk factors such as dyslipidemia, hypertension, donor and recipient age, allosensitization, frequent cellular-mediated rejection and AMR, donor cigarette use, retransplant and the absence of induction therapy [4, 102, 103]. Recipient age is an important risk factor for CAV; infants had the lowest risk and adolescents had the highest [4]. A rejection episode within the first year of transplant is associated with a higher incidence of CAV 3 years post-transplant [4]. The risk was not associated with graft ischemic time or calcineurin inhibitors [4].

Intravascular ultrasound to detect CAV has size limitations in children and hence coronary angiography remains the gold standard. Detection rates are higher when angiography is performed for symptomatic patients compared to asymptomatic patients. However, most cases are detected during routine angiography [102]. Once detected, survival outcomes are poor with 50% mortality 10 years after diagnosis and a 5-year mortality of >66% when CAV is diagnosed in the presence of

symptoms or signs [102]. The risk of graft failure is increased when CAV is detected angiographically in the presence of RAP > 12, PCWP > 15, or EF < 45% [104]. Although the overall reduction in CAV in the recent era may be associated with reduced rates of rejection, more routine use of statins, and early use of mTOR inhibitors, there are no proven therapies that can halt or reverse this process. Retransplantation is the most suitable option for advanced diffuse disease.

Infection

Infection is a significant cause of morbidity and mortality, particularly in the first 12 months after transplantation when immunosuppression is greater [4]. The most common types of serious infection are bacterial (60%), cytomegalovirus (18%), other viral (13%), fungal (7%), and protozoal (2%) [105]. Bacterial, protozoal, and fungal infections commonly involve the respiratory tract or sternal wound. Viral infections increase the risk of graft rejection, and Epstein–Barr virus is associated with lymphoproliferative disease.

At 5-year follow-up, infant recipients had higher occurrence rates of severe and chronic infections compared with older recipients, and the infections were more resistant to treatment. Additionally, the incidence of autoimmune disorders (commonly autoimmune cytopenias) was noteworthy [106].

Malignancy

Although there is an increased risk of malignancy in children after heart transplantation, the risk is low. Freedom from malignancy was >90% in 10-year survivors. Sixteen percent of survivors developed a malignancy by 15 years post-transplant [4]. Most malignancies are lymphatic in origin. Many post-transplant lymphoproliferative disorders (PTLDs) respond to reduction in immunosuppression.

KEY POINTS: HEART TRANSPLANT: MORTALITY RISK FACTORS

- Measures of pretransplant acuity:
  - ECMO
  - renal dialysis
  - mechanical ventilation
- Congenital heart disease
- Retransplantation
- Increasing body mass index.
  - Overall improved after heart transplant survival despite increasing case complexity related to improved perioperative care and optimizing modifiable risk factors.

Renal dysfunction

Acute renal dysfunction may occur in the immediate postoperative period, probably because of the cumulative negative effects of a chronic low CO, CPB, venous congestion, and nephrotoxic drugs. Renal dysfunction increased from 6 at 1 year to 17% at 10 years. However, the need for renal transplant was seen in only 1% by 10 years and freedom from severe renal dysfunction (defined as serum Cr > 2.5 mg/dL) was approximately 90% at 9 years [4]. The risk of developing severe renal dysfunction differs with age at transplant. At 10 years post-transplant, 2.4% of patients transplanted during infancy versus 14% transplanted at age 11–17 years developed severe renal dysfunction [4]. A similar age-related finding is seen in freedom from renal replacement therapy [4]. Multivariable analysis from ISHLT registry data has shown that CHD and retransplant are independently associated with developing renal dysfunction 5 years post-transplant compared with DCM [6].

Other risk factors for chronic renal insufficiency included pretransplant dialysis, HCM, and African American race. Adjusted risk of death in those who developed chronic renal insufficiency was ninefold higher than in those who did not [107]. Renal-protective bundles as mentioned earlier are important.

Other complications

The percentage of recipients with hypertension increased over time to 72% at 10 years post-transplantation. The only medication significantly associated with hypertension was prednisone. Hyperlipidemia also increased steadily to 38% at 10 years after transplantation. There continues to be a lack of consensus on whether abnormal cholesterol values should be treated empirically with statins or whether target ranges for intervention should be established.

Serious gastrointestinal complications have been reported in 18% of recipients (median post-transplant follow-up was 3 years). Complications included (in order) pancreatitis, cholecystitis, recurrent abdominal infection, malignancy, and intestinal pneumatosis. Half of the patients with complications required abdominal surgery [108].

Children with CHD who required extensive reconstruction of vessels during transplantation may develop stenoses at anastomotic sites (e.g. aorta, pulmonary veins). This can usually be relieved by interventional catheterization techniques, but some cases may require surgery.

Quality of life

Most pediatric recipients are rapidly rehabilitated, and full-time attendance at school is achieved in almost all patients within a few months of transplantation. Approximately 50% of children do not require hospitalization in the first year after transplantation. Rejection and infection are the major causes for hospitalization. The functional status of survivors is excellent. The percentage of survivors without functional limitation was 93% at 1 year and 95% at 5 and 10 years. Less than 1% required total assistance. Preadolescent children exhibited "catch-up" growth in height and weight after transplantation. Failure of linear growth was correlated with steroid requirements [4].

Formal exercise testing reveals that maximum capacities for physical work and peak HR are only approximately two-thirds of predicted. A longitudinal assessment found low-peak aerobic capacity and diastolic dysfunction [109], although perhaps less so in infants [110].

A review of cognitive and psychological outcomes after pediatric heart transplantation found that recipients generally functioned within the normal range on most measures of cognitive function [111]. About 20% experienced significant symptoms of psychological distress during the first year after transplantation [112]. Post-traumatic stress disorder seems to be relatively common in parents of pediatric heart transplant recipients [113].

Evidence indicates that children with CHD should be considered separately because they have significantly lower scores on IQ and neurodevelopmental tests when compared with a normative sample [114]. Transition of care from a pediatric to adult heart transplant program needs to start well before the child reaches teen years. Outcomes are impacted by poor transitions [115].

Anesthetic management of children who have undergone heart transplantation

Patients may present for surgery because of complications from cardiac transplantation (e.g. infection, malignancy, drug adverse effects), or the indication for surgery may be unrelated to heart transplantation. Successful anesthetic management requires consideration of the patient's medical status, the physiology of the transplanted heart, and the implications of immunotherapy. These have been discussed earlier.

Future prospects

Donor shortage remains a frustrating problem and is the primary limitation to the number of transplants performed. Efforts to further the care of children with end-stage cardiac disease can be broadly categorized as described in the following sections.

Alternative therapeutic modalities

Research continues on the development of small, implantable VADs suitable as destination therapy or as a bridge to recovery for children of all ages [40]. Another avenue of intensive research is cell-based engineering to replace damaged or dysmorphic heart tissue [116]. In animal models, intravenous injections of bone marrow-derived mesenchymal stem cells readily express phenotypic characteristics of cardiac myocytes, localize at sites of myocardial injury, prevent tissue remodeling, and improve cardiac recovery. When provided with a scaffold such as a prefabricated matrix or decellularized heart tissue, stem cells can localize, differentiate, and function [116]. Heart muscle patches, heart valves, and perhaps the entire heart may in the future be engineered in the laboratory [116].

Improving current therapeutic modalities

Opportunities abound for further refinement of existing therapies. These include reexamination of the allocation of donor organs, ethical analysis of the practice of retransplantation (which is associated with a poor outcome) [18], extended donor organ criteria, better protocols for highly sensitized patients, improved understanding of the timing of interventions such as mechanical ventricular assist (balancing the risks of intervention against the benefit of preserved end-organ function), miniaturization of pediatric CPB circuits, efforts to reduce the side effects of immunosuppression and increase immunotolerance, better therapies to diminish the likelihood of acute and chronic rejection, and improved patient/family support and transitions to enhance compliance with care [117]. Identifying best practices with multiinstitute collaboration and learning networks will help move the field forward [118].

Pediatric lung transplantation

Lung transplantation surgery is a relatively uncommon surgery in the pediatric age group, offered at few centers globally as a life-extending measure for children with irreversible, end-stage, vascular, or parenchymal lung disease. Compared to adults, the experience with pediatric lung transplantation remains modest. Since 2007, the number of centers performing pediatric lung transplant surgery and transplant surgeries performed annually has remained relatively constant (Figure 32.11) [119]. Thirty-seven centers across the world perform approximately 100 lung transplant surgeries annually in children [120]. The outcomes of pediatric lung transplantation, although comparable to adults, remain worse than other solid organ transplant surgeries [121]. Numerous unique challenges related to the patient's medical condition, donor–recipient match, development, and growth of the transplanted organs can affect the long-term outcomes after pediatric lung transplant surgery.

Indications, contraindications, and listing criteria in children

The majority of pediatric lung transplant recipients are between the ages of 11 and 17, and only 20% of lung transplant surgeries are performed in children 6–11 years of age. Generally, lung transplant surgery is considered a treatment for any end-stage lung disease. Indications for listing a child for lung transplant surgery vary by age (Table 32.8) [122]. Overall, cystic fibrosis (CF) remains the most common indication in older children whereas pulmonary hypertension is the common reason for lung transplantation in children aged 1–5 years. Only a handful of transplant centers offer lung transplant surgery to infants and neonates. Common indications for severe irreversible respiratory failure in neonates include congenital and acquired diseases such as surfactant protein (B and C) deficiency, interstitial lung disease, pulmonary vein stenosis, pulmonary hypoplasia, and alveolar capillary dysplasia. In the United States, the OPTN is a federal government agency that regulates organ transplantation. OPTN data for 2020 and 2021 suggest a dramatic decrease in transplantation for CF, despite an overall stable number of lung transplants for all age groups. In the 11- to 17-year-old age group, lung transplants for CF decreased from about 20 $year^{-1}$ in the United States, from 2000 to 2019, to only 3–4 $year^{-1}$ in 2020–2021 (Table 32.9) [123]. The overall number of pediatric lung transplants has also decreased, with almost all of the decrease attributable to the decrease in the 11- to 17-year-old age group.

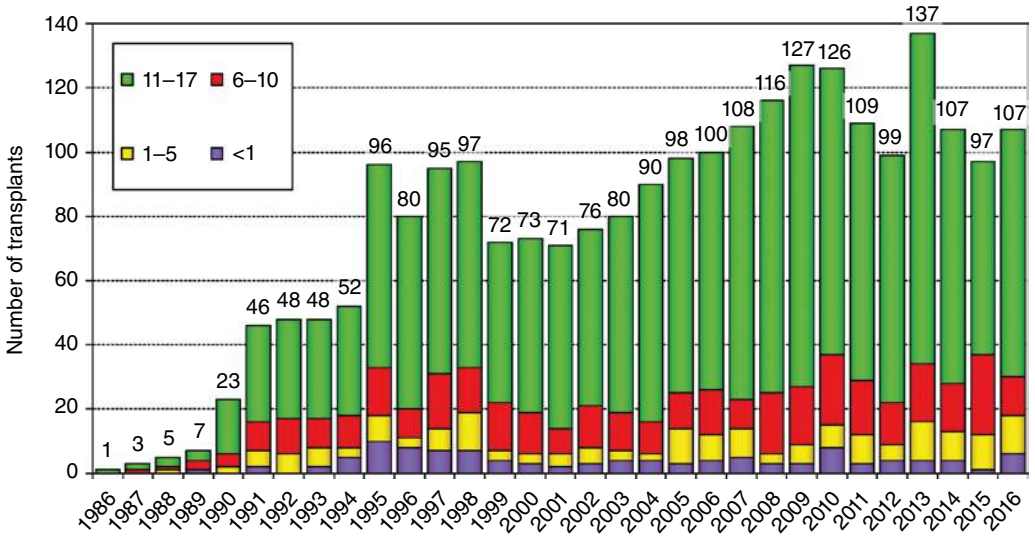


Figure 32.11 Annual pediatric lung transplant surgery volume with age distribution reported to the International Society of Heart Lung Transplantation. (Source: Goldfarb et al. [119]. Reproduced with permission of Elsevier.)

Table 32.8 Indications for pediatric lung transplants by recipient age group (transplants: January 1, 2000, to June 30, 2016)

Diagnosis	<1 Year No. (%)	1–5 Years No. (%)	6–10 Years No. (%)	11–17 Years No. (%)
Cystic fibrosis	0	4 (3.7)	116 (50.0)	814 (66.7)
Non–cystic fibrosis-bronchiectasis	0	0	2 (0.9)	23 (1.9)
ILD	5 (8.3)	9 (8.3)	6 (2.6)	37 (3.0)
ILD other	6 (10.0)	10 (9.3)	21 (9.1)	46 (3.8)
PH /pulmonary arterial hypertension	7 (11.7)	28 (25.9)	24 (10.3)	100 (8.2)
PH				
Eisenmenger syndrome	0	1 (0.9)	2 (0.9)	6 (0.5)
Other	15 (25.0)	21 (19.4)	8 (3.4)	20 (1.6)
Obliterative bronchiolitis (non-retransplant)	0	10 (9.3)	26 (11.2)	58 (4.8)
Bronchopulmonary dysplasia	4 (6.7)	4 (3.7)	3 (1.3)	3 (0.2)
ABCA3 transporter mutation	5 (8.3)	4 (3.7)	1 (0.4)	1 (0.1)
Surfactant protein B deficiency	13 (21.7)	4 (3.7)	1 (0.4)	0
Surfactant protein C deficiency	0	1 (0.9)	0	1 (0.1)
Retransplant				
Obliterative bronchiolitis	0	4 (3.7)	8 (3.4)	41 (3.4)
Not obliterative bronchiolitis	0	4 (3.7)	6 (2.6)	41 (3.4)
COPD, with or without A1ATD	2 (3.3)	1 (0.9)	3 (1.3)	10 (0.8)
Other	3 (5.0)	3 (2.8)	5 (2.2)	20 (1.6)

Source: Based on from Goldfarb et al. [122].

A1ATD, α-l-anti-trypsin deficiency; ABCA3, adenosine 5′-triphosphate–binding cassette subfamily A member 3; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PH, pulmonary hypertension.

Cystic fibrosis

CF is an autosomal recessive disorder caused by mutations in a single gene. These mutations cause loss of function of cystic fibrosis transmembrane conductance regulator (CFTR) protein, which affects the epithelial cells in the lungs, gastrointestinal tract, pancreas, sweat glands, and male reproductive system. So far, more than 2,000 gene mutations have been identified. The core CFTR mutation reduces chloride and bicarbonate in the airway secretions and decreases the water content in the airway epithelial layer. These changes result in thick mucus secretions that are the hallmark of CF. These secretions produce obstruction, persistent inflammation, and superimposed infections of the airways. The ciliary function of the epithelial layer is also depressed (Figure 32.12) [124, 125]. Approximately 10% of CF patients have associated liver and pancreatic

Table 32.9 Lung transplant indications in the United States, 2017–2021

Age Groups	Diagnoses	2017	2018	2019	2020	2021* (projected)
All, <1 year to 65+ years	All	2,449	2,530	2,714	2,539	2,619 (projected)
	CF	263	263	246	78	48 (projected)
<1 year	All	3	2	4	7	4–5 (projected)
	CHD					
	CF					1
	Other	3	2	3	6	2–3
	IPF					
	PPH			1	1	
	Retransplant					
1–5 years	All	4	1	4	3	3 (projected)
	CHD					
	CF			1		
	Other	4		2	2	3
	IPF					
	PPH		1	1	1	
	Retransplant					
6–10 years	All	5	7	5	3	1–2 (projected)
	CHD					
	CF	2	0	1	1	
	Other	3	5	3	2	
	IPF					
	PPH		2	1		1
	Retransplant					
11–17 years	All	32	25	37	19	12 (projected)
	CHD					
	CF	23	20	22	4	3 (projected)
	Other	6	4	10	11	6 (projected)
	IPF	1				
	PPH	2	1	4	4	3 (projected)
	Retransplant			1		

Data source: U.S. Organ. Procurement and Transplant Network [123]
CF, cystic fibrosis; CHD, congenital heart disease; IPF, idiopathic pulmonary fibrosis; PPH, primary pulmonary hypertension; *2021 data represents 8 months, January 1 to August 31, 2021.

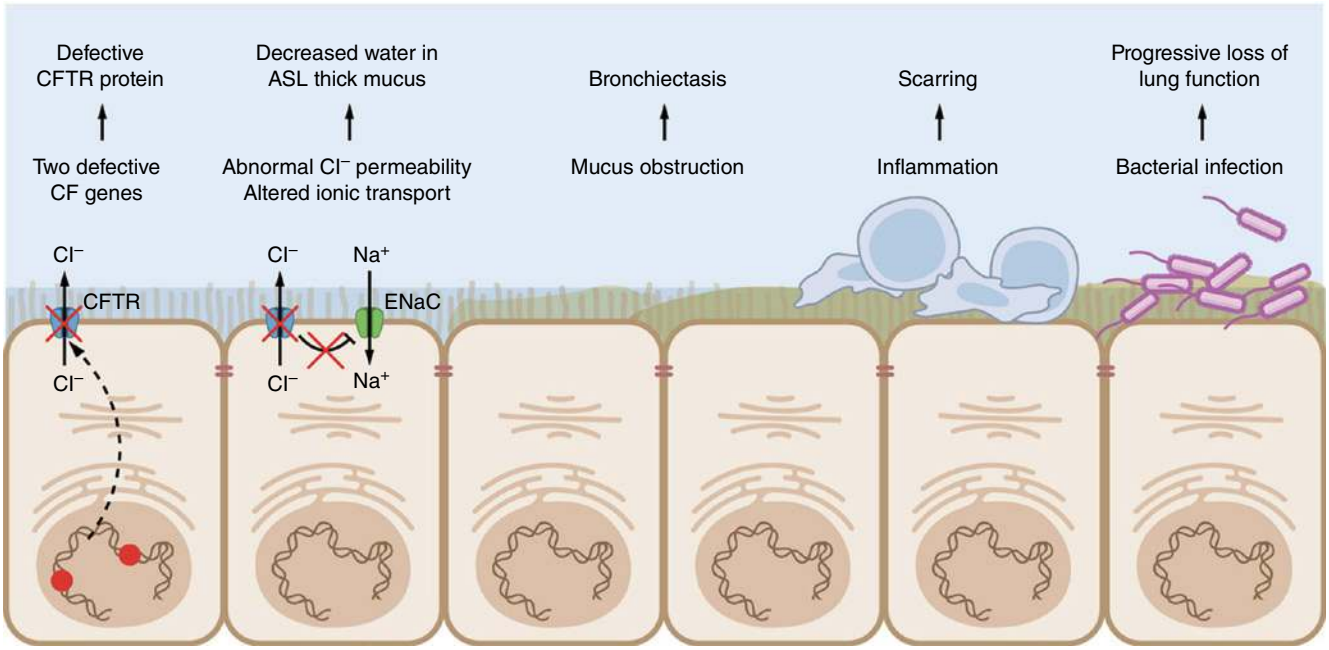


Figure 32.12 The cystic fibrosis (CF) pathogenesis cascade in the lung. The mechanism of CF dysfunction starts with the primary CFTR gene defect and ultimate leads to severe lung deficiency. CFTR, cystic fibrosis transmembrane conductance regulator; ASL, airway surface liquid; ENaC, epithelial Na^+ channel. (Source: Amaral [124]. Reproduced with permission of John Wiley & Sons.)

disease related to the same mutation, resulting in clinically significant pancreatic insufficiency and malabsorption of key nutrients.

The treatment of CF has significantly improved during the past two decades, and in the current era, most children born with CF are expected to survive into adulthood [125]. Improved abilities to diagnose the disease early, the introduction of multidisciplinary care, and the use of newer targeted therapies have resulted in better preservation of lung function in patients with CF. The core treatment aims to improve mucus clearance by increasing hydration of the airway secretions using saline and mannitol nebulization. Recombinant human DNAse-1 use also improves ciliary clearance by decreasing mucus viscosity [126].Drugs such as Ivacaftor and Lumacaftor target specific genetic mutations and have been approved for clinical use [127, 128]. These drugs have been shown to improve lung function, increase body mass index, minimize infections with *Pseudomonas*, improved glucose tolerance, and reduce the number of lung infections. Unfortunately, these drugs target specific mutations seen in approximately 40–50% of patients and are remain extremely expensive [129].

Despite the maximal therapy, a few children suffer from repeated pulmonary infections with multidrug-resistant bacteria and develop irreversible respiratory failure. For these children, lung transplant surgery becomes the only viable treatment option. A significant and rapid decline in the clinical status despite the maximal therapy should trigger a referral to a transplant center.

Life expectancy in CF has continued to improve, and in the current era is 46.2 years, due to widespread routine newborn screening, publication of evidence-based guidelines to optimize nutrition and pulmonary health, and also the development of CF-specific interdisciplinary care centers [130]. As noted above, the CFTR modulator therapies, which can be classified as potentiators, correctors, and amplifiers, have significantly changed the progression of CF lung disease and are among the primary reasons why fewer CF patients are reaching end-stage lung disease in teenage and early adult years [131]. In 2019, the U.S. Food and Drug Administration approved a triple-drug combination therapy, elexacaftor/texacaftor/ivacaftor, for patients aged 12 years and older that will allow almost 90% of CF patients to have a highly effective therapy. CF-related liver disease results in cirrhosis in approximately 3% and occasionally leads to combined lung–liver transplantation.

Pulmonary hypertension

Severe pulmonary hypertension can occur in diverse group diseases that affect children of all age groups. The progression of clinical symptoms and prognosis depend on the underlying condition. As a diagnosis, pulmonary hypertension is the second most common indication for lung transplantation in children, but for neonates, younger children, and infants, it is the most common indication for lung transplant surgery. In contrast, for older children aged 6–17 years, pulmonary hypertension accounts for 7–8% of lung transplant surgeries [132]. Medical treatment of pulmonary arterial hypertension has improved considerably. Newer medications, such as endothelin receptor antagonists (bosentan), phosphodiesterase inhibitors (sildenafil), and prostacyclin analogs, have improved 5-year survival to more than 80% [133]. These drugs reduce the pulmonary arterial pressure and possibly reverse long-standing changes in the pulmonary vascular architecture. Many children eventually fail maximal medical therapy, and for those patients, lung transplantation remains the only treatment option available. Atrial septostomy has been advocated as a temporizing measure, to improve symptoms and serve as a bridge to transplant, although whether this procedure confers a survival advantage is less clear [134]. More recently, many centers have offered a palliative Potts shunt (a pulmonary systemic central shunt from descending aorta to left PA) to decompress the right ventricle, prevent right ventricular failure, and prolong life. In small series, mid-term survival outcomes and functional status after Potts shunt surgery were similar to patients after lung transplant surgery [135]. For children who develop irreversible pulmonary hypertension secondary to a congenital cardiac defect, the complexity of cardiac lesion dictates the decision to perform lung transplant versus HLT. See Chapter 33 for further discussion of pulmonary hypertension.

Neonatal and infant lung transplant

Few pediatric lung transplant centers have offered lung transplant surgery in very young children. According to the 2017 report of the ISHLT registry, slightly more than 100 patients younger than 1 year of age have undergone lung transplant surgery [122]. The underlying diseases resulting in severe respiratory failure for infants and neonates are different. The major indications for lung transplant surgery in very young children include genetic mutations in the surfactant proteins (B and C), bronchopulmonary dysplasia, CHD, congenital diaphragmatic hernia, and pulmonary dysmaturity. For these patients, severe respiratory failure presents early in life and requires mechanical ventilation and extracorporeal life support [136].

Lung transplant listing criteria

The criteria for listing children for lung transplant surgery are based on the progression of the underlying disease, functional status of the patient, and expected improvement in the quality of life (Table 32.10). It is challenging to develop survival models for rare and uncommon diseases. In the past, a life expectancy of less than 2 years was used for listing a child for lung transplant surgery. Listing a patient for lung transplant surgery is a complex, shared decision-making process that involves numerous conversations among patients, their families, pediatric pulmonologists, pediatric cardiothoracic surgeons, and social workers. Many clinical and social factors such as nutritional status, functional status, patient and family ability to comply with immunosuppressant treatment, and move geographically close to a transplant center are considered.

For CF patients, the international consensus guidelines consider numerous clinical factors such as rate of decline in forced expiratory volume in 1 second (FEV_1) to less

than 30%, elevated $PaCO_2$ (>50 mmHg), decreasing PaO_2 (<60 mmHg), frequency of hospitalizations, and decreasing distance on the 6-minute walk test [137, 138]. For pulmonary hypertension patients, progressive disease, despite the maximal medical therapy, generally initiates a conversation about transplant surgery as a treatment option. Because pulmonary hypertension in pediatric patients can progress rapidly, children should be referred to a transplant center early. Criteria recommended by the International Society of Heart and Lung Transplantation Society include New York Heart Association class III or IV, cardiac index of less than 2 L/min/m^2, and mean right atrial pressure less than 15 mmHg, but are more suitable for adult patients [139]. High plasma levels of biomarkers, such as von Willebrand factor and brain natriuretic peptide, may suggest severe disease [140, 141].

Active malignancy, sepsis, tuberculosis, neuromuscular disease, heart failure, and acquired immunodeficiency syndrome (AIDS) are considered absolute contraindications for any transplant surgery (Table 32.11). On rare occasions, patients with severe renal or hepatic disease may be considered for lung and hepatic or renal transplants. Previously, based on adult data, colonization of the trachea with *Burkholderia cenocepacia* or nontuberculous *Mycobacteria* was considered an absolute contraindication [143]. More recently, some centers have shown that some children with this multidrug-resistant bacterial infection can be successfully transplanted. In patients with pulmonary hypertension, a compromised ventricular function is considered a relative contraindication.

KEY POINTS: INDICATIONS, CONTRAINDICATIONS, AND LISTING CRITERIA

- CF has historically been the most common indication, until recently accounting for >50% of pediatric lung transplants. Effective CF drugs have decreased the numbers of end-stage CF patients requiring transplantation.
- Pulmonary hypertension is the second most frequent indication and is the most common indication for transplant in children <5 years of age.
- Neonatal and infant lung transplants surgeries are uncommon; indications include congenital cardiac defects, pulmonary hypertension, and genetic mutations in surfactant protein synthesis.
- Life expectancy <2 years is a criterion for lung transplant; active malignancy, sepsis, multiorgan failure, neuromuscular disease, and AIDS are contraindications.

Donor management and lung preservation

As with other organ transplants, donor availability has been a limiting factor in offering lung transplant surgery to a larger number of patients. Children face longer wait times and, as a result, children have higher mortality rates while waiting for the organs compared to adults. Only about 15–30% of the cadaveric donor lungs are considered acceptable for transplantation. In the United States, donor organs

Table 32.10 Recommendations regarding timing of referral to lung transplant center

Specific disease	Timing of referral
Surfactant deficiencies	Patients with SP-B deficiency and ABCA3 deficiency with refractory respiratory failure should be referred immediately Patients with SP-C deficiency and less severe forms of ABCA3 deficiency may respond to medical therapy and should be referred when unrelenting progression of disease develops
Primary pulmonary hypertension	Patients who present in NYHA class III or IV or have evidence of right heart failure should be referred immediately Patients who fail to respond adequately to vasodilator therapy should also be referred
Eisenmenger syndrome	When the trajectory of pulmonary hypertension appears to be worsening with impaired exercise tolerance and worsening quality of life
Other pulmonary vascular disorders (pulmonary vein stenosis, alveolar capillary dysplasia)	These patients should be referred immediately since they typically do not respond to medical management and are at risk for sudden death
Cystic fibrosis	Patients with percent predicted FEV_1 values less than 30%, frequent hospitalizations, refractory hypoxemia, or hypercapnia should be referred for transplant
Bronchopulmonary dysplasia	Patients with recurrent or severe episodes of respiratory failure or evidence for progressive pulmonary hypertension
Diffuse parenchymal lung disease	Patients without evidence for systemic disease that could affect outcome should be referred early

Source: Sweet [142].

FEV_1, forced expiratory volume in 1 second; NYHA, New York Heart Association; SP, surfactant protein.

Table 32.11 Contraindications to pediatric lung transplantation

Absolute	Relative
Active malignancy	Pleurodesis
Sepsis	Renal insufficiency
Active tuberculosis	Markedly abnormal body mass index
Severe neuromuscular disease	Mechanical ventilation
Documented, refractory nonadherence	Scoliosis
Multiple organ dysfunction	Poorly controlled diabetes mellitus
Acquired immunodeficiency syndrome	Osteoporosis
Hepatitis C with histological liver disease	Hepatitis B surface antigen positive
	Fungal infection/colonization
	Chronic airway infection with multiple resistant organisms

Source: Faro et al. [143]. Reproduced with permission of John Wiley & Sons.

are allocated by the OPTN. A new lung allocation system, implemented in 2005, uses a patient's medical condition as the primary determinant of organ allocation and discourages the use of waiting time [145]. Under this system, a lung allocation score (LAS) is calculated for children older than 12 years. Multiple variables such as age, functional status, forced vital capacity (FVC), and oxygen requirement are used for calculating the LAS. The new policy also mandates that the donor lungs from donors less than 18 years of age are preferentially given to pediatric patients [145]. A two-tier priority system based on medical urgency was implemented in 2010 for children younger than 12 years of age. Since its implementation, there has been a reduction in the total number of listed patients, median time to transplant, and waiting list mortality without affecting survival after the surgery [146, 147]. Consequently, the listed patients and recipients at the time of surgery are sicker [148]. Additional changes in the lung allocation system were made in 2017, and as a result, all donor lungs below the age of 18 years are now directed to the children younger than 12 years listed within the same geographical area. Efforts to increase the size of the donor organ pool include the use of organs from extended criteria donors, relaxing size-matching guidelines, using donors after circulatory death, the use of ABO-I transplants in children under 2 years of age, and the use of ex vivo lung perfusion techniques to retrieve organs from geographically remote areas [149].

Donor lungs are selected after a thorough medical screening, and multiple laboratory tests are conducted to rule out any lung pathology or infection. In younger children, comparable age and height with less than 20% discrepancy are considered an acceptable match. An ideal donor is younger than 55 years, a nonsmoker, and has no cardiopulmonary or significant neurological disease history. The donor lungs should produce good gas exchange ($PaO_2 > 350$ mmHg with FiO_2 of 1.0) on a moderate amount of ventilatory support. The chest radiograph and bronchoscopy should rule out any significant infection, consolidation, or malignancy. Ideally, the donor's lungs are accepted only if the ischemic time is expected to be less than 6 hours. Over the past decade, selection criteria for ideal donor lungs have been relaxed [150]. Extended criteria donors with mild lung disease, history of smoking, age above 55 years of age, and mild chest trauma are accepted if the recipient's condition is rapidly deteriorating.

The pool of donors is not limited to brain-dead donors. Organs from the DCD have been used in the adult lung transplant patients, and 1- and 5-year survival in these patients appear to be similar to those who received lungs from brain-dead donors [151]. In addition, normothermic ex vivo lung perfusion techniques are being evaluated to increase the number of suitable grafts. This technique maintains normal physiological status and allows cells to stay metabolically active, thus prolonging the window for transplantation [152].

Efforts to preserve lung function after the determination of death may reduce the incidence of primary graft failure and improve long-term graft function. Ventilation with tidal volumes of 6–8 mL/kg along with aggressive hemodynamic management while restricting fluid to maintain central venous pressures of 4–6 mm has been shown to optimize pulmonary function of the donor lungs [150]. The process of harvest includes systemic heparinization of the donor and infusion of prostaglandin E_1 into the main PA. Lungs are inflated with $FiO_2 < 0.4$ to an airway pressure less than 20 cm H_2O. Lungs are removed en bloc with descending aorta, left atrial cuff, main PA, and thoracic aorta.

Bridge to transplantation

While waiting for the surgery, some patients rapidly deteriorate and require supportive care to bridge the transplant. Infants and neonates have the most extended wait times and, therefore, have the highest mortality while on the waiting list. Almost one-third of the listed children end up requiring ventilatory support while waiting for their transplant surgery. For a few patients, mechanical ventilation fails to ensure adequate gas exchange or oxygenation and use ECMO is needed. However, the use of ECMO has significant morbidity before the transplant surgery, and post-transplant outcomes for these patients remain poor. To minimize the consequences of ECMO, in select patients with low PVR, a paracorporeal lung assist device (PLAD) has been used. The surgery involves redirecting the PA blood flow to the left atrium through an external oxygenator (Novalung GmbH, Germany or the Quadrox-iD Pediatric oxygenator, MAQUET GmbH & Co KG, Germany) without using a pump [153] (see Figure 32.13). Ambulatory ECMO, with veno-venous (VV) or veno-arterial (VA), has also been described to support end-stage lung disease patients as a bridge to transplant [154, 155]. As noted above, another method to bridge some patients to transplant, or avoid lung transplant, is using Potts shunt surgery as an alternative treatment for children with end-stage pulmonary hypertension. Creating a central shunt between the PA and descending aorta can unload the right ventricle, preserve right ventricular function, and extend life. [135, 156]. The preliminary reports suggest that 1-year survival after Potts shunt results is reported to be similar to that after lung transplant.

KEY POINTS: DONOR MANAGEMENT, LUNG PRESERVATION, AND BRIDGE TO TRANSPLANT

- Only 15–30% of donor lungs are considered acceptable; the new LAS, based on medical urgency, is calculated for every patient >12 years of age.
- Children < 12 years of age receive organs based on two-tier waiting list.
- Acceptable gas exchange, "clear" bronchoscopy and chest radiograph, and anticipated ischemic time <6 hours are the usual criteria for donor lungs.
- ECMO, PLADs, and Potts shunt surgery are used as a bridge to transplant in critically ill patients.

Anesthetic management and surgical approach

When listing for lung transplantation, children undergo extensive evaluation, including a visit to the preoperative clinic. Routine testing includes ECG, echocardiogram, pulmonary function tests, arterial blood gases, and complete metabolic panel. Children diagnosed with pulmonary hypertension also undergo a cardiac catheterization where the response to oxygen and nitric oxide is tested and cardiac anatomy is defined. Associated comorbid conditions are optimized. Approximately 10% of CF patients have associated liver and pancreatic disease. Malnutrition due to CF liver disease is associated with worse post-transplant outcomes, and aggressive efforts to improve the nutritional status of CF patients either by the placement of gastrostomy tube or use of parenteral nutrition are often warranted. Chronic antibiotic therapy often results in renal tubular damage and electrolyte disturbances.

Anesthetic management is dictated primarily by the patient's underlying condition. At the time of the match, many patients are at home without the need for oxygen supplementation. An increasing number, especially neonates and infants, are critically ill and require mechanical ventilation and often extracorporeal mechanical support. Like other organ transplant surgeries, the time of surgery is unpredictable. Standard nil per os (NPO) guidelines are followed to minimize the risk of aspiration and contamination of the new lungs. Propofol and etomidate are safe in hemodynamically stable patients, but ketamine may be the preferred drug for inducing children with high pulmonary pressures. Anesthesia is maintained with inhalational agents and supplemented with opioids, midazolam, and muscle relaxants. The airway is secured with a cuffed endotracheal tube, including for those with an existing tracheostomy. Lung isolation is rarely used for pediatric lung transplant surgery. Selective pulmonary vasodilators such as iNO and prostacyclin analogs are continued through the pre-CPB period.

Historically, sequential bilateral lung transplant surgery is performed through a trans-sternal, clamshell incision, though some surgeons have promoted a mid-sternotomy approach. Bilateral pneumonectomies require extensive dissection, which is often complicated by excessive adhesions from previous infections and thoracic surgeries. Antifibrinolytic drugs such as tranexamic acid or aminocaproic acid have become standard of care. Ensuring adequate ventilation and oxygenation during the pre-bypass period can be challenging. Copious

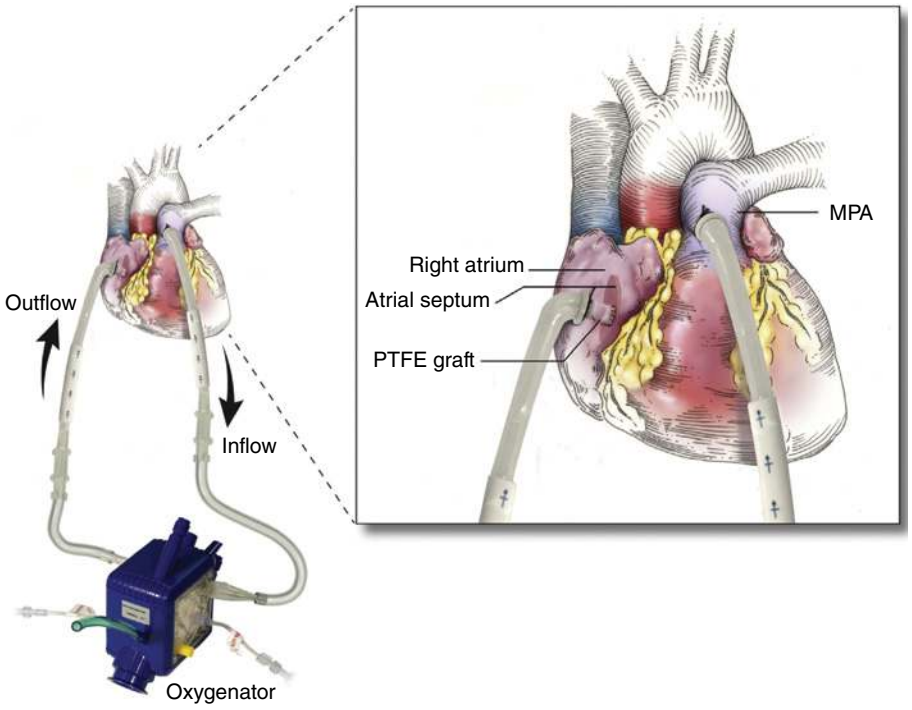


Figure 32.13 The Maquet Quadrox-iD membrane oxygenator is used for paracorporeal lung assist in neonates and infants. A PTFE graft is used to extend a pediatric Berlin Heart cannula through the right atrium and to the interatrial septum for outflow to the left atrium. MPA, main pulmonary artery; PTFE, polytetrafluoroethylene. (Source: Hoganson et al. [153]. Reproduced with permission of Elsevier.)

Table 32.12 Summary of intraoperative considerations for pediatric lung transplantation

Pre-bypass
- Consider pathophysiology of lung disease: CF, PH, CHD, others
- Maintain all pulmonary vasodilator therapy on schedule
- Administer immunosuppressant induction agents and antibiotics according to preoperative plans
- Standard single-lumen TEE for most cases. Plan with surgeon for tracheostomy management
- Vascular access: arterial line (consider femoral if arms up for clamshell incision), CVP, large-bore PIVs
- Discuss surgical approach: BSLT (clamshell incision, separate bronchial anastomoses) vs. en bloc technique with bronchial revascularization (sternotomy, single tracheal anastomosis)
- Ventilate to baseline $PaCO_2$ values (e.g. hypercarbia common)
- ICU ventilator or HFOV may be required for infants
- Maintain pulmonary toilet pre-bypass: suction, bronchodilators
- Prepare for possibility that donor lungs are unsuitable after visualization (limit fixed agents, reverse muscle relaxant, awaken patient, remove lines)

Bypass period
- Normally mild-moderate hypothermic bypass
- Repair any congenital cardiac lesions, e.g. ASD
- Normally no aortic cross-clamp
- Instill antibiotics into trachea for CF patients
- Prepare bronchoscope to visualize bronchial/tracheal anastomoses, suction/irrigate blood, mucus, clot
- Ideally ischemic time goal is <6 hours until lungs reperfused (completed pulmonary artery anasotomoses)

Post-bypass period
- Separate from bypass on ventilator settings that minimize volutrauma, barotrauma, oxygen toxicity: 6–7 mL/kg (donor weight), peak pressure < 25 cmH_2O), PEEP 5 cmH_2O, FiO_2 0.4–0.5 or less
- iNO 20 ppm, epoprostenol frequently used
- Limit fluid administration (no lymphatic drainage): CVP 4–6
- Milrinone, vasopressors (vasopressin, phenylephrine) as needed
- Significant bleeding treated with platelets, cryoprecipitate/fibrinogen concentrate, fresh-frozen plasma/coagulation factor concentrate/activated factor VII
- Consider TEE: intracardiac repair, pulmonary venous anastomoses, PA anastomoses, ventricular function, pulmonary hypertension
- Early graft dysfunction (hypoxemia, pulmonary edema) treated with increased FiO_2, PEEP, iNO to maintain SpO_2 in low 90 second; veno-venous ECMO if needed
- Usually will not extubate in OR; but stable patients can be extubated in 12–24 hours
- Full handoff report from anesthesia/surgical team to ICU team
- Pain management via opioid infusion, dexmedetomdine, patient/nurse-controlled analgesia

CF, cystic fibrosis; PH, pulmonary hypertension; CHD, congenital heart disease; BSLT, bilateral sequential lung transplantation; HFOV, high-frequency oscillatory ventilation; ASD, atrial septal defect.

lung secretions, poor lung compliance, and surgical manipulation of the lung tissue require close vigilance to the patients' ventilatory status. Aggressive ventilation should be avoided in patients with chronic hypercarbia, and ventilation parameters are adjusted to ensure normal pH levels. Significant bleeding is expected during the pre- and post-bypass period. Large-bore venous access and blood products are needed.

All pediatric lung transplant surgeries are performed with the assistance of a CPB machine or ECMO. Invasive monitoring of arterial blood pressure and central venous pressure is a routine. Lung transplant surgery is a class I indication for intraoperative TEE and is used to monitor ventricular function and postoperative pulmonary hypertension and evaluate vascular anastomoses.

Several unique factors make the use of CPB necessary for pediatric lung transplant surgery. In CF patients, the use of CPB allows the resection of both lungs simultaneously and minimizes the risk of contamination of the new lungs. Smaller children are physically too small to accommodate even the smallest double-lumen endotracheal tube. Others with significant pulmonary hypertension, neonates, and infants are often too tenuous to tolerate single lung ventilation. In addition, the use of CPB provides stable hemodynamic conditions during the extensive surgical dissection, greatly simplifies surgical management, and consequently reduces ischemic times. The use of CPB, however, comes with its own risks. Generation of inflammatory mediators and activation of complement cascade during CPB contribute to the ischemic–reperfusion injury to the implanted lungs. More recently, based on the experience in adult patients, VA ECMO has been successfully used to PGD secondary to CPB and reduce postoperative bleeding [157]. Mild hypothermia or normothermia is needed for implanting donor lungs. The use of aortic cross-clamping is rarely warranted unless a correction of an existing intracardiac defect is needed. After establishing CPB, both lungs are removed by ligating and dividing pulmonary arterial, atrial cuff, and bronchial connections (Figure 32.14) [158]. A second surgical team simultaneously prepares the donor lungs. To reduce bacterial contamination of the new tracheobronchial tree, native tracheal stump is irrigated with a concentrated solution of antibiotics such as tobramycin. The implantation of the new lungs begins with an end-to-end bronchial anastomosis. As bronchial blood supply is compromised during the procedure, peribronchial tissue is wrapped around the anastomotic site to enhance healing. Vascular supply to the new lungs is established by an end-to-end PA anastomosis. The pulmonary veins are reconnected to the recipient's left atrium en bloc, using the donor's atrial cuff. Before weaning off the CPB machine, an aggressive pulmonary toilet and visualization of the bronchial anastomosis with a fiberoptic bronchoscope are performed to ensure adequate ventilation.

Ventilator parameters, guided by the donor weight, are titrated to ensure that lungs are well expanded. Trauma to the new ling, caused by overdistension of the new lungs, increases endothelial permeability and potentiates PGD. iNO is routinely used to induce pulmonary arteriolar vasodilation and improve ventilation-perfusion mismatch. A focused TEE helps assess the adequacy of major vessel anastomoses. The transplant surgery disrupts native lymphatic drainage of the donor lungs and their ability to clear intra-alveolar secretion. Judicious fluid management, with a goal of maintaining central venous pressure within 4–6 mmHg range, is recommended.

All patients are electively ventilated during the immediate postoperative period, but many are extubated on postoperative

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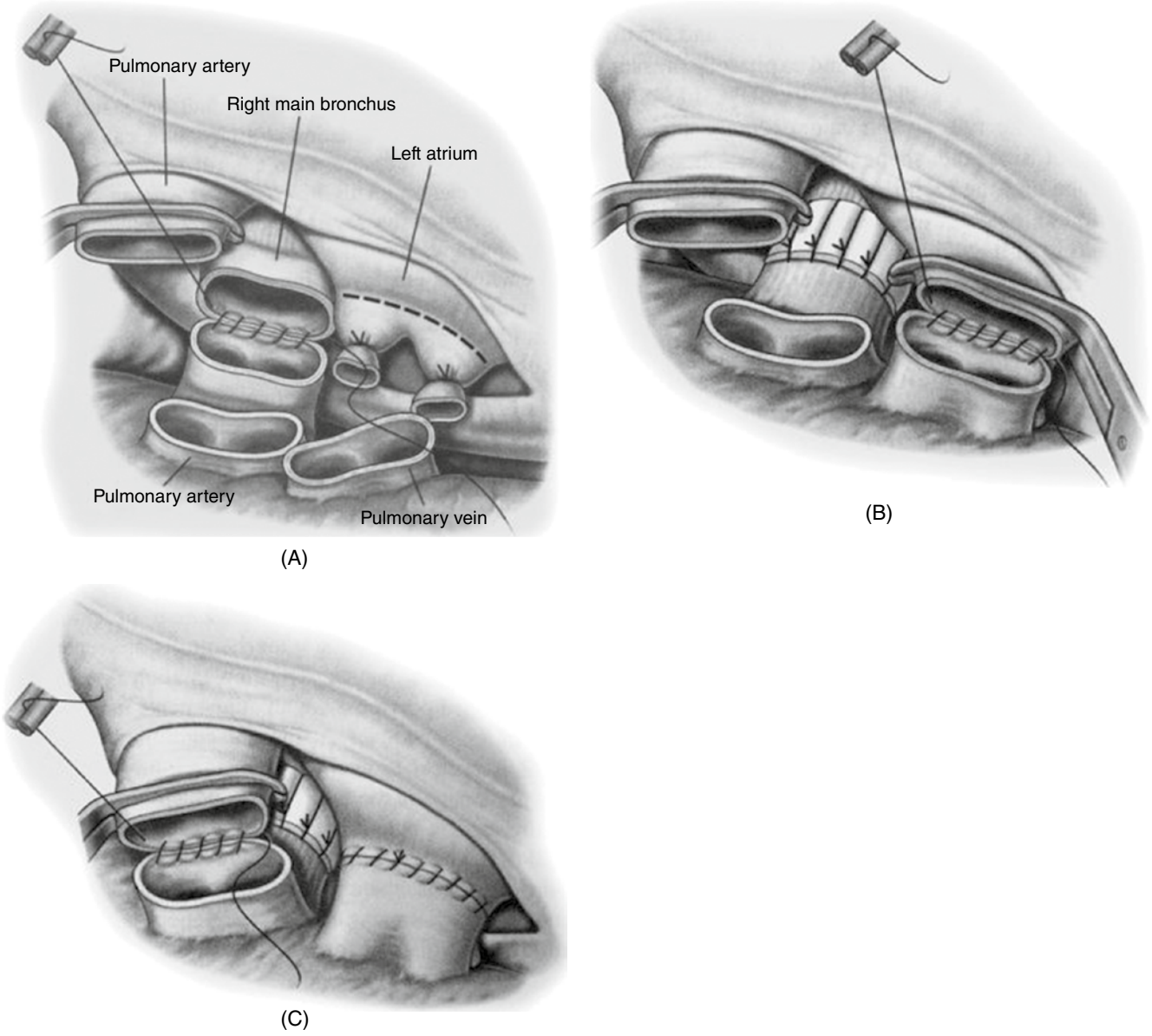


Figure 32.14 (A). End-to-end right bronchial anastomosis. (B). End-to-end right pulmonary vein anastomosis. (C). End-to-end right pulmonary artery anastomosis. (Source: Nigro et al. [158]. Reproduced with permission of John Wiley & Sons.)

day 1. Infants and neonates have a more protracted recovery and have prolonged ventilatory needs (median 24 vs. 3 days) [159] Postoperative pain relief is usually accomplished by patient-controlled analgesics and narcotic infusions. Regional anesthesia with an epidural catheter is recommended for older children. Epidural catheters, or other regional techniques such as erector spinae plane catheters, may be placed used 24–48 hours after the surgery when the coagulation parameters have normalized. (See Chapter 24 for a discussion of regional anesthetic techniques for cardiothoracic surgery). Table 32.12 summarizes the intraoperative considerations for anesthesia for pediatric lung transplantation.

Another surgical technique that has been described is the en bloc technique with a single tracheal anastomosis and bronchial artery revascularization using a using a cuff of donor aorta [160]. This approach is performed through a median sternotomy. A potential advantage of this technique is better perfusion to the graft because the bronchial artery circulation normally provides half of the airway's dual blood supply. Theoretically, this could reduce airway and infectious complications and delay the onset of bronchiolitis obliterans syndrome, which can have an ischemic etiology. The descending aorta is clamped with a partial occlusion clamp, and the bronchial artery button is anastomosed to it (Figure 32.15) [160]. After reperfusion of the bronchial arteries, bleeding will be observed from the cut edge of the trachea, and blood return can often be seen in the PAs and pulmonary veins. In theory, this could limit further graft ischemia. A single end-to-end tracheal anastomosis is completed, followed by flexible bronchoscopy by the anesthesiologist for removal of bloody secretions. During aortic cross-clamp, a single left atrial anastomosis is

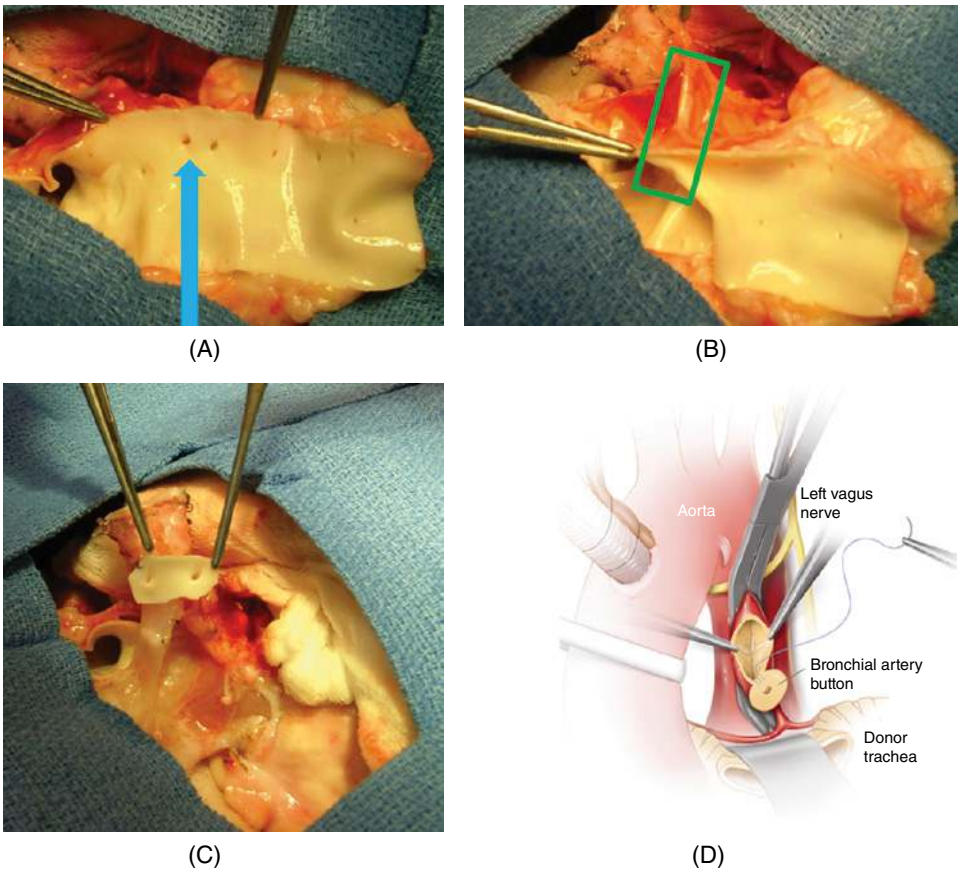


Figure 32.15 Key operative aspects involving bronchial artery revascularization technique: (A) the descending donor thoracic aorta is opened longitudinally; (B) the bronchial artery is identified arising from the aorta; (C) aortic button containing the origin of two bronchial arteries; esophagus previously removed; (D) suturing the bronchial arteries to the aorta. (Source: Guzman-Pruneda et al. [160]. Reproduced with permission from Elsevier.)

performed, and other intracardiac anomalies may be addressed. After removal of the aortic cross-clamp, an end-to-end main PA anastomosis is performed. In a single-institution comparison study of 88 bilateral sequential lung transplants (BSLTs) and 31 en bloc lung transplants (EBLT) with bronchial artery revascularization, there were no differences in bypass or ischemic times, early or longer term survival, graft dysfunction, or cellular rejection scores. BSLT was associated with higher ischemic injury and non-airway complications.

Living donor lobar transplant (LDLT) involves two living donors, each of them donating a lower lobe to the recipient. LDLT had been used to provide organs rapidly to children with CF who underwent an unexpected rapid progression of their disease, which, in the modern era, is less frequent, as noted above. Although outcomes can be comparable to deceased donor transplant [161], and there is some evidence to suggest that the incidence of bronchiolitis obliterans is lower in LDLT recipients [162], the procedure is resource intensive and has ethical implications because 10–20% of donor lobectomy surgeries have serious complications [163, 164]. The 2017 ISHLT report noted the number of LDLT surgeries in pediatric recipients peaked in 1998–1999 and since then has decreased substantially, and none were reported in 2013–2015 [165].

When the recipient's chest is too small to accommodate the donor lungs, the donor lungs can be reduced in size. Options include lobectomy (typically, the right middle lobe or lingula), wedge resection using a linear stapler, single lobe transplant, or split lung "bipartitioned" transplant (in which two smaller "lungs" are created from a single deceased donor lung). Reports suggest that outcomes in pediatric recipients of reduced-size organs can be comparable to recipients of full-sized grafts [166, 167].

KEY POINTS: ANESTHETIC MANAGEMENT AND SURGICAL APPROCH

- The preoperative condition ranges from stable at home to chronic ventilation with a tracheostomy to mechanical support on a bridge to transplant device.
- CPB and the bilateral sequential lung transplant techniques are used for essentially every pediatric lung transplant.
- Ventilation parameters after CPB include limiting inflation pressures and volumes (chosen for the donor lungs), limiting FiO_2 to maintain SpO_2 at 90–95%, and addition of iNO.

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Immediate perioperative complications

Primary graft failure

PGD is a syndrome of acute lung injury that presents within the first week of surgery. In its most severe form, it presents as fulminant pulmonary edema with persistent and severe hypoxemia immediately after reimplantation of the new lungs. The PGD can be seen in approximately 30% of patients and remains a major factor for early and possibly delayed mortality after pediatric lung transplantation. Other potential reversible causes of hypoxemia, such as inadequate ventilation, right ventricular dysfunction, and right-to-left shunt, must be ruled out before the diagnosis of PGD is made.

Vascular endothelium makes up a vast portion of the lung parenchyma. This metabolically active endothelium of the donor lungs is continuously exposed to oxygen during the entire ischemic period, leading to free radicals-related injury and graft failure. The time course of this complication suggests two distinct but complementary mechanisms. The first phase, seen immediately after the reperfusion, is initiated by the donor macrophage-induced release of superoxide anions, inflammatory cytokines, mast cell degranulation, and complement activation. These humoral and cellular mediators damage the integrity of the vascular endothelium and cause movement of fluid to the interstitial and alveolar space. Clinically, this presents as progressive hypoxemia with copious, pink frothy secretions that are not amenable to the conventional treatment methods such as diuresis or positive end-expiratory pressure (PEEP). The release of inflammatory cytokine induces the recruitment of the recipient's neutrophils to the injury site and initiates the delayed phase of PGD within hours after the initial injury. During the late phase, neutrophils produce reactive superoxide anions and hydroxyl ions and greatly amplify the initial injury, causing further damage to the pulmonary endothelium. Neutrophils also produce elastase and block the blood flow in the capillaries, resulting in architectural damage to the lung tissue [168]. Since 2005, ISHLT has implemented a common system grading the severity of the reperfusion injury. This system is based on serial measurements of PaO_2/FiO_2 ratio and the presence or absence of infiltrates consistent with pulmonary edema on chest X-ray [169] (Table 32.13). Based on adult lung transplant patient data, donor factors such as female gender, African American race, age (<21 or >45 years), and positive history of smoking may be associated with increased risk of PGD. Longer Ischemic time is also considered an important factor associated with the development of PGD [170].

Table 32.13 Recommendations for grading of primary graft dysfunction (PGD) severity

Grade	PaO_2/FiO_2	Radiographic infiltrates consistent with pulmonary edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Source: Christie et al. [169].

The preventive strategies to reduce the incidence of PGD are mainly focused on improving lung preservation techniques, reducing ischemic time, improving donor management, and minimizing barotrauma. Surgeons routinely allow ejection of a small amount of blood into the PA immediately after establishing the vascular supply to the first lung. Empirical evidence suggests that the prophylactic use of pulmonary vasodilators like PGE_1 and prostacyclin may reduce the incidence and severity of the reperfusion injury. The preventative role of iNO, however, is less clear. There have been few randomized clinical trials, and they have failed to demonstrate the efficacy of prophylactic administration of iNO in preventing primary graft failure. The treatment of PGD is supportive and includes mechanical ventilation, restriction of fluids, and the use of inotropes. For most patients, PGD resolves over few days, but some patients require ECMO support. VV ECMO can provide adequate oxygenation and gas exchange for few days. PGD is associated with a protracted postoperative course and significantly higher early mortality. A retrospective study that included both adult and pediatric patients reported significantly higher mortality in patients who developed primary graft failure. PGD has also been independently associated with bronchiolitis obliterans.

Bleeding

The anesthesia team must expect and prepare for significant bleeding during the pre-and post-bypass periods. Patients who had previously undergone thoracic surgeries or had suffered multiple bouts of infections are expected to have difficult dissection during the pneumonectomy phase. Bleeding is also a major concern in patients who were initially palliated with reverse Potts shunt for pulmonary hypertension as the transplant surgery requires the ligation of the shunt before the initiation of the cardiopulmonary pass.

Physiological changes and growth of the transplanted lungs

Denervation of the lungs is a consequence of transplant surgery. Sensory afferent and efferent neurons connect lungs and brainstem and regulate airway smooth muscle tone and breathing [171]. The physiological consequences of denervation on the transplanted lungs are not fully understood. Few clinically significant effects on the airway reflexes, mucociliary movement, and bronchial hyperreactivity have been reported [172]. The lack of afferent stimuli to the respiratory center can result in poor coordination between thoracic and abdominal muscles – a frequently observed finding during the immediate postoperative period. Adult lung transplant patients show a subnormal increase in minute ventilation with carbon dioxide challenge [173]. Beyond the loss of neural control, transplantation also causes a complete disruption of the lymphatic drainage. During the first postoperative week, transplanted lungs remain more susceptible to interstitial edema. Spontaneous recovery of the lymphatic system has been documented in animal models [174]. The long-term clinical implications of lymphatic injury are poorly understood, but its role in immune response and bronchiolitis obliterans is being investigated.

Serial pulmonary function tests, radiological findings, histological evidence, and clinical examination suggest that donor lungs from younger infants and neonates continue to grow after the surgery. This growth occurs in both lung parenchyma and the larger airway and mirrors the somatic growth of the recipient. Cohen et al. observed that functional reserve capacity increases along with somatic growth [175]. This increase accompanies a similar increase in the FEV_1, suggesting that the growth in the lungs results from an increase in the number of alveoli and not from mere distension of existing alveoli. The lobar lungs transplanted from mature, living-related donors also demonstrate a similar growth pattern. However, morphometric studies suggest that the number of alveoli in these lobar lungs remains constant, and the observed growth in lung volume results primarily from alveolar distension [176]. The measurement of diffusing capacity for carbon monoxide (DLCO) provides an estimate of gas exchange surface area. Serial measurements of DLCO support the opinion that the increase in lung volume seen after mature lobes is secondary to hyperinflation.

KEY POINTS: PRIMARY GRAFT FAILURE, PHYSIOLOGICAL CHANGES, AND SURVEILLANCE

- PGD develops during the first week of transplant surgery and presents with varying degrees of hypoxemia and pulmonary edema.
- Addition of PEEP, diuresis, inotropic support, and VV ECMO are support modalities.
- Transplanted lungs continue to grow in infants and children, in both larger airways and lung parenchyma, including an increase in the number of alveoli.
- Serial pulmonary function tests and bronchoalveolar lavage with biopsies are performed as routine surveillance monitoring.

Surgical complications

Airway complications

In the current era, airway complications are uncommon. Bilateral sequential lung transplant approach without bronchial artery revascularization disrupts the blood supply to the donor bronchus. This may lead to poor healing at the anastomotic site and other airway complications such as the development of granulation tissue, airway stenosis, tracheomalacia, and, rarely, airway dehiscence. Surgical techniques such as the use of peribronchial tissue around the anastomotic site and the use of a smaller segment of donor bronchus can minimize the incidence of these complications. In a single-center study involving 239 transplant surgeries, Choong et al. reported that 13% of children needed surgical interventions for their airway complications [177]. Preoperative bacterial and fungal infections, longer ischemic times, and prolonged mechanical ventilation were identified as significant risk factors. In this study, the younger age of the patient was not identified as an independent risk factor for developing airway stenosis. However, infants may have a higher incidence of tracheomalacia and dynamic obstruction of major airways. Most patients with tracheobronchomalacia show significant improvement without any surgical interventions but may need prolonged mechanical ventilation [178]. Usually, airway complications are diagnosed within the first 3 months of surgery. Airway stenosis is usually treated successfully with repeated mechanical balloon dilatation through a rigid bronchoscope. Children with recurrent airway stenosis after repeated balloon dilations may require mechanical stents to maintain airway patency. A 2018 consensus statement by the ISHLT provided standardized definitions for airway complications in adult and pediatric lung transplant recipients and proposed standardized treatment approaches [179].

Vascular anastomotic complications

Vascular anastomotic complications are rare, mostly related to the pulmonary veins. Significant pulmonary venous obstruction presents immediately after weaning off bypass or in the immediate postoperative period. Clinical signs include persistent hypoxemia and frothy pink secretions in the airway, along with increased pulmonary arterial pressures. Postoperative perfusion scans are routinely performed to rule out any discrepancy in the pulmonary blood flow. If a pulmonary venous obstruction is suspected, a definitive diagnosis can be made during cardiac catheterization. Significant obstruction in the PA anastomosis usually requires urgent surgery.

Nerve injuries

Phrenic, vagal, and recurrent laryngeal nerves lie adjacent to the bronchopulmonary tree, and injury to these nerves during the transplant surgery is frequent. Huddleston reported a 22% incidence of phrenic nerve injury in children [178]. The resulting diaphragmatic paralysis is usually a transient phenomenon but can prolong the need for mechanical ventilation and intensive care stay. Injury to the vagus nerve leads to gastroesophageal reflux, and the incidence of gastric paresis can be as high as 50%. Severe gastric paresis and recurrent silent aspiration have been implicated in deteriorating graft function and bronchiolitis obliterans. Younger patients are especially susceptible to this injury, and many neonatal and infant lung recipients require fundoplication after their transplant surgery. Patients with deteriorating pulmonary function have been shown to benefit from surgical treatment of gastroesophageal reflux. Injury to the recurrent laryngeal nerve (mostly left) and resulting vocal cord dysfunction are seen in 10% of children. Most of these children will recover without any residual vocal cord defects [178].

Arrhythmias

Atrial suture lines are a potential source for abnormal depolarization and repolarization. Clinically significant atrial flutter requiring medical treatment is seen in about 11% of pediatric patients. Supraventricular tachycardia and atrial fibrillation are also seen. Most arrhythmias are amenable to medical treatment alone.

KEY POINTS: SURGICAL COMPLICATIONS

- Airway stenosis, tracheomalacia, granulation tissue, or dehiscence is seen in approximately 13% of pediatric lung transplant recipients.
- Pulmonary vein obstruction is a serious complication heralded by hypoxemia and frothy pink secretions.
- Phrenic nerve, recurrent laryngeal nerve, and vagus nerve injuries are relatively frequent complications after lung transplantation in children.

Medical complications

Graft rejection, immune therapy, and drug interactions

Recurrent graft rejections are more common after lung transplantation compared with other solid organ transplant surgeries. Lungs have a large endothelial surface and contain immunologically active cells, making them more susceptible to immune-mediated rejection when compared with the other solid organs. Hyperacute rejection, mediated by preexisting antibodies to donor HLA, is uncommon and can be prevented by virtual crossmatching where the transplant recipients are screened for antibodies against donor HLA. Acute rejection is common and affects almost all transplant patients within 3 months of the surgery. Infants and younger children appear to be somewhat protected and suffer from fewer episodes of acute rejection [180]. This discrepancy could be explained by their relatively immature immune system. More recently, the role of anti-HLA antibodies in graft rejection has been investigated. The clinical picture of rejection is a nonspecific deterioration in the functional status or pulmonary function parameters and is almost clinically indistinguishable from the infectious process. Any decline in clinical status or pulmonary function tests is further investigated by transbronchial lung biopsy. Once the diagnosis of acute rejection is made, these episodes are treated aggressively with a course of intravenous drugs such as high-dose steroids, antithymocyte globulin, and tacrolimus.

After the induction immunotherapy (IL-2 receptor antagonists or a polyclonal antibody), triple-drug therapy with a combination of a calcineurin inhibitor (tacrolimus), cell-cycle inhibitor (MMF), and corticosteroid (prednisone) is continued for the first year. Side effects related to the chronic use of these drugs include compromised renal function, hypertension, hypercholesteremia, hirsutism, and osteoporosis. About 30% of children have clinically significant renal dysfunction, but others demonstrate subclinical renal dysfunction with borderline serum Cr levels. As many transplant recipients are at risk of developing renal failure, nephrotoxic drugs such as nonsteroidal anti-inflammatory agents are avoided even if renal function is normal. Cystic patients, because of the unreliable gastric absorption and hepatic clearance, are at risk for developing acute toxicity from oral medications like cyclosporine. In fact, the high incidence of central nervous complications like seizures, headaches, and stroke has been attributed to acute increases in plasma levels of cyclosporine. Hepatic enzymes such as cytochrome P450 metabolize commonly used immunosuppressant drugs. Drugs that are commonly used during surgery (e.g. metoclopramide, barbiturates) induce cytochrome P450, resulting in dangerously low levels of cyclosporine.

Opportunistic infections and antibiotic prophylaxis

The risk of viral and bacterial infection remains high throughout the life span of the recipient, but the risk is the highest during the immediate postoperative period. Viral infections are more commonly seen in infants and toddlers. Immunosuppression combined with poor mucociliary clearance, poor cough efforts, and disrupted lymphatics make newly transplanted lungs potential sites for infections. Bacterial infections are the most common, but fungal and viral infections tend to have higher mortality. Cytomegalovirus, adenovirus, Epstein–Barr virus, and influenza are common viral infections. Cytomegalovirus infection is associated with an increased incidence of acute and chronic rejection. Treatment of cytomegalovirus pneumonitis requires 2–3 months of treatment with intravenous or oral ganciclovir. Some patients are prescribed prophylactic trimethoprim/sulfamethoxazole to prevent *Pneumocystis jirovecii* pneumonia. Preoperative infection with aspergillosis is often seen in CF patients, requiring prolonged treatment with antifungal drugs such as voriconazole.

Post-transplant lymphoproliferative disorder

Overall, the incidence of malignancy in the post-transplant period is more than 10% at 5 years. PTLD remains the most common form of malignancy. PTLD is strongly associated with Epstein–Barr virus and results from B-cell proliferation and is commonly seen in patients with T-cell depletion [181]. The hyperplasia of the lymphatic tissue is mostly seen in intrathoracic tissue as lung nodules and mediastinal lymphadenopathy, but it can also present in extrathoracic tissues, such as tonsillar hypertrophy, and cerebral and visceral masses. Most children will respond to a reduction in immunosuppression, but treatment with monoclonal antibodies and steroids may be needed in a few unresponsive patients.

Chronic lung allograft dysfunction

Chronic allograft dysfunction is responsible for poor long-term survival after lung transplant surgery. Bronchiolitis obliterans (BO), the most common type of chronic lung allograft dysfunction (CLAD), is the leading cause of death beyond the first year of survival. Roughly, half of the surviving children develop BO by 5 years after their lung transplant surgery [122]. In addition to increasing mortality, CLAD causes significant morbidity and impairs quality of life after lung transplant. The hallmark of the disease is progressive fibrosis and slow obliteration of the small airways. BO is a histological diagnosis reflecting inflammatory and fibroproliferative changes in the bronchioles. The exact mechanism of BO is unknown, but recent research suggests that both immune-mediated and immune-independent mechanisms are responsible. Alloimmune-mediated mechanisms cause injury by acute rejection, cellular lymphocytic bronchiolitis, activation of the humoral immune system, and autoimmune dysfunction. Immunity-independent mechanisms such as

infections, aspiration, ischemia, and primary graft failure also appear to contribute to progressive destruction of the pulmonary architecture. Injury caused by these mechanisms induces a significant fibrotic reaction, remodeling, and abnormal angiogenesis. Routine transbronchial biopsies are not reliable early diagnosis. The clinical manifestation, called bronchiolitis obliteration syndrome, should be strongly suspected in children where a more than 20% decrease in FEV_1 is noticed in the absence of infection or rejection. A subgroup of CLAD that does not demonstrate restrictive function may stabilize with aggressive treatment with azithromycin and photopheresis. In a retrospective analysis, children with a total ischemic time of less than 2 hours had a significantly lower incidence of BO when compared with a similar group of patients with longer ischemic time (20 vs. 52%) [182]. The incidence of BO is also lower in smaller children (age <3 years at the time of transplant). This is presumably related to a lower annual incidence of acute rejection compared with the older children (0.2 episodes compared with 1.95) [159]. Enhanced immunosuppression is the cornerstone of currently used therapies, though none of the methods have been able to show a consistent benefit to all patients. Antireflux surgery may also prevent or even reverse the decline in pulmonary function in some patients. Statins have the ability to induce apoptosis in fibroblasts and may hold a promise in treating BO. Retransplantation has become more common in older patients, but short- and long-term survival benefits are limited after retransplant surgery.

KEY POINTS: MEDICAL COMPLICATIONS

- Infants and young children have fewer episodes of acute rejection, explained by a relatively immature immune system; these episodes are heralded by nonspecific deterioration in functional status.
- Opportunistic infections with bacteria, viruses, and fungi are a constant threat.
- PTLD is usually due to Epstein–Barr virus and is seen in about 8% of patients.
- BO is the leading cause of death after the first year and is the major threat to long-term survival.

Surveillance

These children are closely monitored for rejection, infection, growth, and BO. Pulmonary function tests, bronchopulmonary lavage, and transbronchial biopsies are performed at frequent intervals. Older children can cooperate to perform spirometric tests, and the values of FEV_1, FVC, and flow-volume loops can be serially measured with reasonable accuracy. In infants and younger children (less than 2 years of age), serial values of peak expiratory flow rates are measured at different values of FRC. Peak expiratory flow rate is measured by rapid inflation, followed by rapid deflation. This is achieved by using mask inflation, followed by a rapid external thoracoabdominal compression. These tests are noninvasive but are physically stimulating and are adversely affected by active patient resistance. Consequently, most of the children require deep sedation and/or general anesthesia for these tests. Any deterioration in the baseline values is further investigated by transbronchial biopsy, bronchoalveolar lavage, and open lung biopsy.

Long-term survival

Overall, long-term survival after a lung transplant in children is improving and remains comparable to adults (5.7 vs. 6.2 years). 56.4% of patients, who received lung transplants after 2008, were alive at 5 years [183].

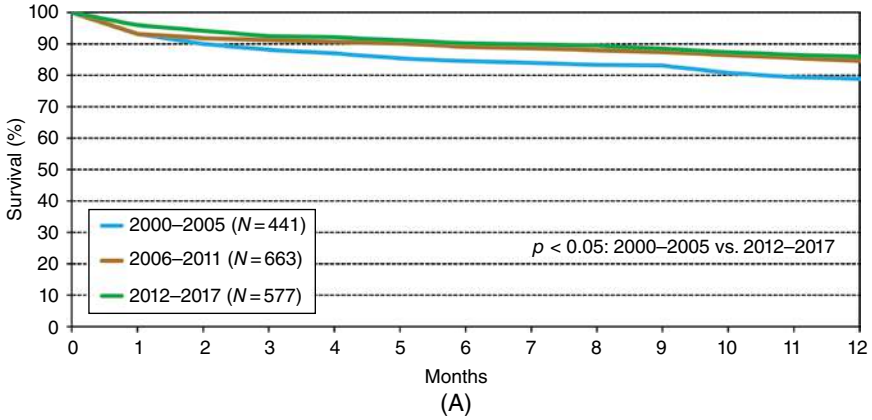
Unfortunately, during the past 30 years, no significant improvement has been observed in 5-year conditional to 1-year survival, suggesting that improvements in care have resulted in a reduction in the earlier mortality. Still, long-term outcomes after lung transplant surgery in children have remained disappointing. Post-transplant survival is better for children younger than 12 years of age. Mortality is the highest during the first year after surgery, and approximately 15% of transplanted children succumb to primary graft failure and infections in the first year (Table 32.14). For those who survive beyond 1 year, infections, CLAD, and PTLD are the common causes of death. Figures 32.16–32.18 present survival data for pediatric lung transplants by age, era, diagnosis, and early/late deaths, as well as freedom from BO [183].

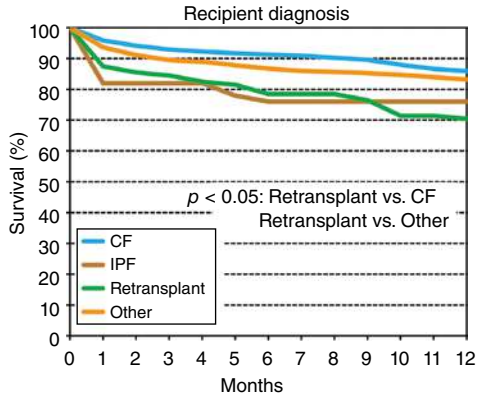
Few prospective studies analyzing the benefit to pediatric patients have been conducted. Liou et al. performed a Cox

Table 32.14 Causes of death after pediatric lung transplantation

Cause of death	0–30 Days (*N* = 130)	31 Days–1 Year (*N* = 204)	>1—3 Years (*N* = 296)	>3–5 Years (*N* = 148)	>5 Years (*N* = 185)
OB/BOS	0	19 (9.3%)	103 (34.8%)	59 (39.9%)	76 (41.1%)
Acute rejection	3 (2.3%)	3 (1.5%)	6 (2.0%)	4 (2.7%)	4 (2.2%)
Lymphoma	0	7 (3.4%)	6 (2.0%)	3 (2.0%)	5 (2.7%)
Malignancy, other	0	3 (1.5%)	1 (0.3%)	2 (1.4%)	7 (3.8%)
CMV	0	5 (2.5%)	0	0	0
Infection, non-cmv	16 (12.3%)	58 (28.4%)	50 (16.9%)	22 (14.9%)	19 (10.3%)
Graft failure	29 (22.3%)	45 (22.1%)	83 (28.0%)	35 (23.6%)	45 (24.3%)
Cardiovascular	21 (16.2%)	9 (4.4%)	4 (1.4%)	1 (0.7%)	2 (1.1%)
Technical	18 (13.2%)	3 (1.5%)	3 (1.0%)	3 (2.0%)	2 (1.1%)
Multiple organ failure	22 (16.9%)	29 (14.2%)	17 (5.7%)	6 (4.1%)	12 (6.5%)
Other	21 (16.2%)	23 (11.3%)	23 (7.8%)	13 (8.8%)	13 (7.0%)

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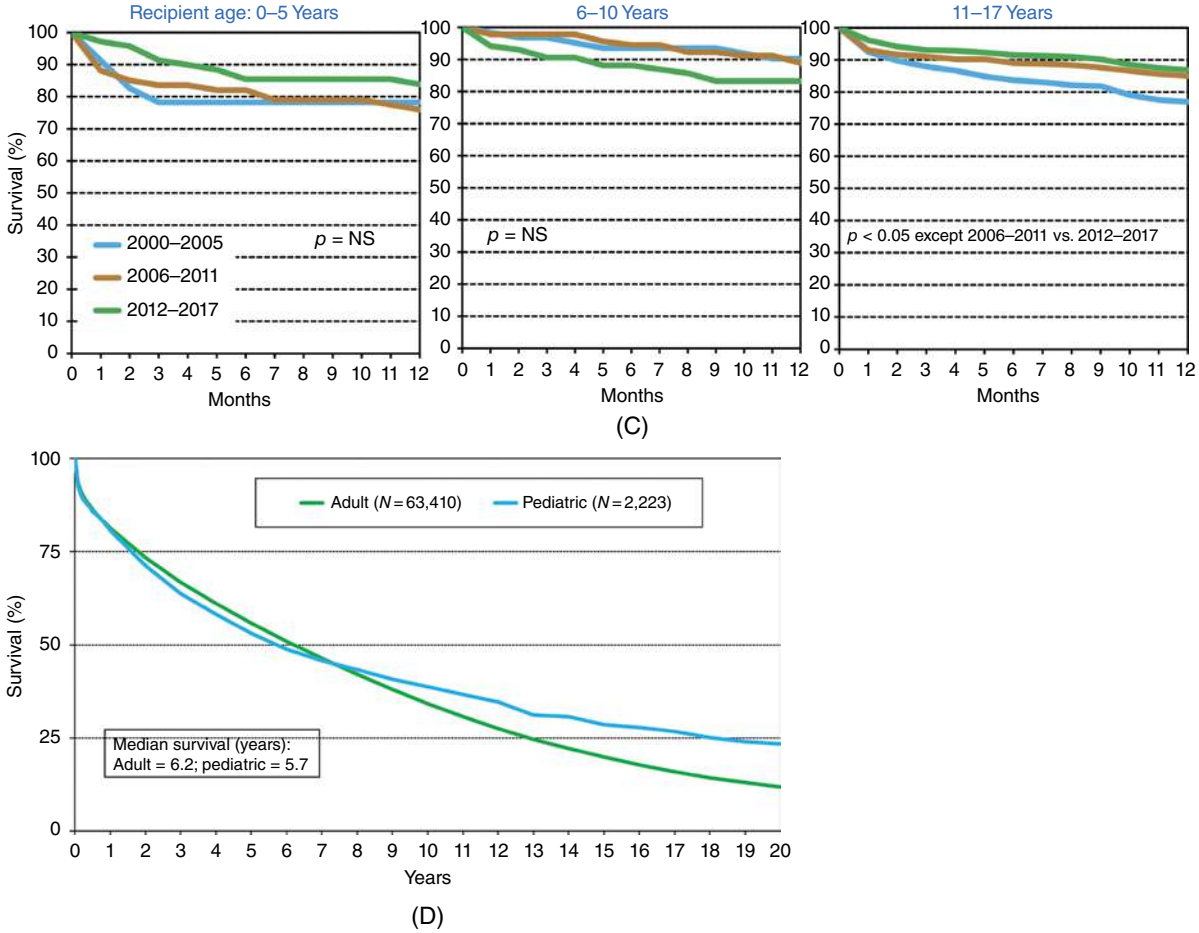


Figure 32.16 A 12-month survival after pediatric lung transplant (0–17 years of age). (A). Survival by transplant era. (B). Survival by recipient diagnosis; CF, cystic fibrosis; IPF, idiopathic pulmonary fibrosis. (C). Lung transplant survival by age and era. (D). Adult vs. pediatric lung transplant overall survival, 1986–2018. (Source: Adapted from Hayes et al. [183].)

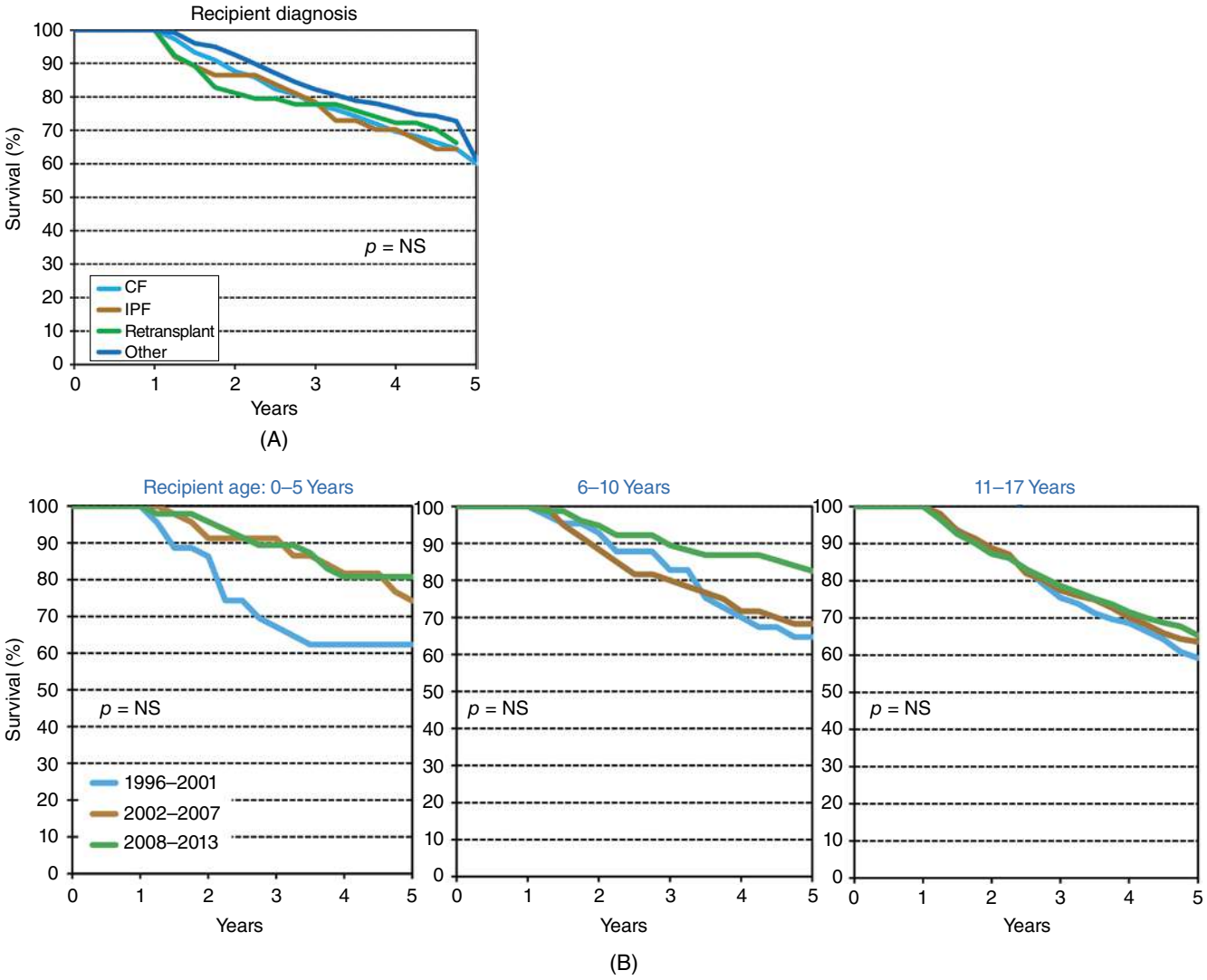


Figure 32.17 Pediatric lung transplant 5-year survival conditioned on survival to 1-year after transplant. (A). Survival by diagnosis. (B). Survival by recipient age and era. (Source: Adapted from Hayes et al. [183].)

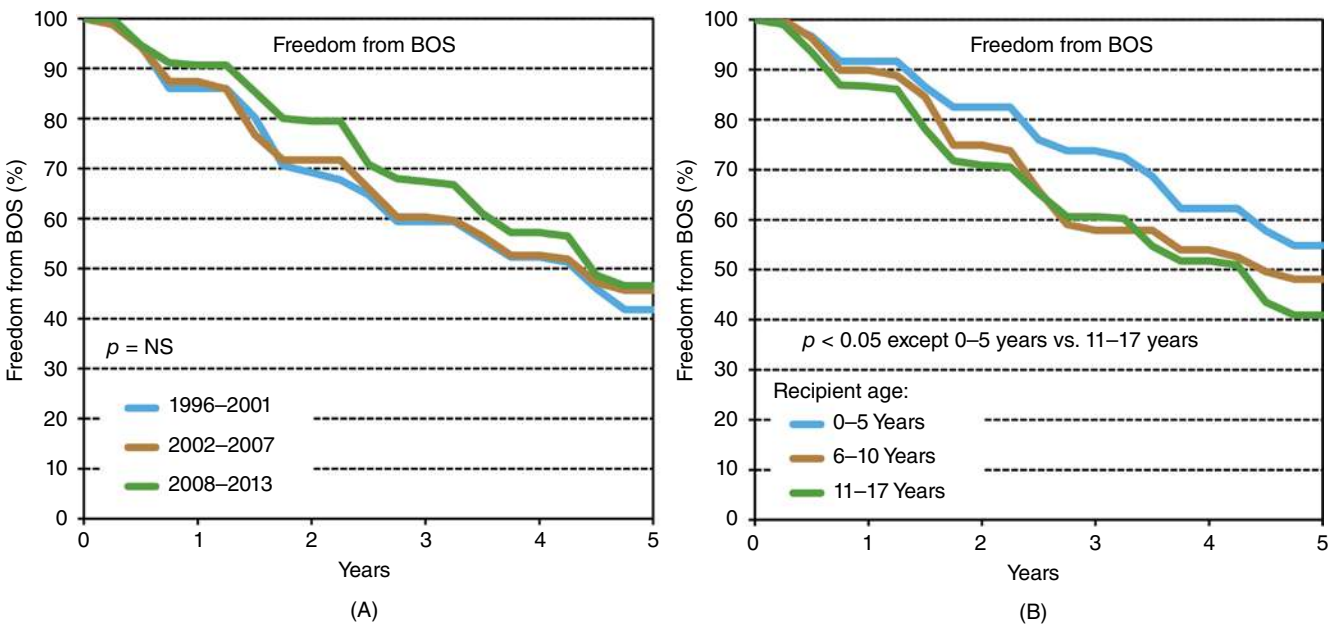


Figure 32.18 Freedom from bronchiolitis obliterans syndrome (BOS) after pediatric lung transplantation. (A) Freedom from BOS by era. (B) Freedom from BOS by age. (Source: Adapted from Hayes et al. [183].)

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proportional hazards analysis in children with CF, using transplant surgery as a time-dependent covariate. The authors observed that, based on the recent data from the OPTN database, children with a 5-year life expectancy of less than 50% at the time of transplant showed no difference from the nontransplanted group with similar severity of the disease. Among 127 children with a 5-year predicted survival greater than 50%, the transplanted group showed a substantial decrease in post-transplant survival when compared with the control nontransplant group. It was concluded that benefit from lung transplantation for CF patients could no longer be assumed [185]. However, the study did not include the impact of the recent changes in the lung allocation system, and the authors were unable to comment on the improvements in the quality of life in CF children after transplant surgery. Another limitation of the study was that it included covariates obtained 2–3 years prior to the surgery and did not account for the medical condition of the patient at the time of transplant. The impact of this highly invasive surgery on the quality-of-life years survived has not been well studied in lung transplant pediatric patients. Future studies are needed to clarify the potential benefit of lung transplant surgery in children with CF and other diseases leading to end-stage pulmonary failure.

KEY POINTS: MORTALITY AND LONG-TERM SURVIVAL

- Overall, pediatric lung transplant survival is worse than other solid organ transplants.
- Median survival since 1990 is 4–6 years, with patients <10 years having longer survival slightly.
- Since 2002, survival has improved slightly in pediatric lung transplant recipients.

Anesthesia for patients with lung transplant surgery

After lung transplantation, pediatric patients will present for routine transbronchial bronchoscopic surveillance, and anesthetic technique is institution-dependent and varies according to the age of the child and function of the lungs. If general anesthesia is required, one technique is to use a laryngeal mask airway, which allows a large diameter airway for bronchoscopic access; topical anesthetic treatment of the larynx and the lower airway is provided by the pulmononologist. Alternatively in older patients, intravenous sedation with any one of a number of agents, with generous topical anesthesia, can be utilized. Noncardiac surgery in this population requires a thorough preanesthetic evaluation, including review of pulmonary function tests, and a plan to continue immunosuppressants, and inhaled and systemic pulmonary dilators. Patients with significant BO can have significantly increased airway resistance and reduced compliance; these patients need to have procedures performed in their lung transplant center with careful multidisciplinary planning involving their transplant pulmonologist.

The COVID-19 pandemic and lung transplantation

SARS-CoV2, the viral etiology of COVID-19 infection, can unleash a severe, destructive inflammatory response that can lead to significant lung damage, destruction of lung tissue, and requirement for mechanical ventilation, mechanical support with VV or VA ECMO, and cause end-stage lung disease that can only be treated with lung transplantation in some cases. Case reports of lung transplantation appeared in mid-2020, and several hundred lung transplants in COVID-19 patients with what was deemed irreversible lung disease have been performed as of late 2021 [186–188]. Significant precautions for personal protective equipment must be taken by the entire surgical team, including at minimum masking with a highly protective medical-grade facemask, e.g., N95 mask, eye protection, double gloving, and gowning, for the entire case. COVID-19 testing of donors and recipients has become the norm in the pandemic era. Concerns arose over the possibility that some patients could harbor latent virus that would be reactivated with the initiation of immunosuppressive regimens. In addition, several reports of COVID-19 infection in lung transplant recipients, and at least one report of COVID-19-positive donor lungs being implanted, have appeared in the medical literature. [189, 190] Long-term survival needs to be determined, and international and U.S. lung transplant registries have added this category of disease to their databases [191].

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Singh TP, Hsich E, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: 23rd pediatric heart transplantation report-2020; focus on deceased donor characteristics. J Heart Lung Transplant 2020;39(10):1028–37. doi: 10.1016/j.healun.2020.07.008. Epub 2020 Jul 24. PMID: 32773323; PMCID: PMC7737222. The 23rd pediatric heart transplant report from the ISHLT registry focuses on patient age. Important topics include geographic trends, diagnosis, survival, and the conventional post-transplant morbidities. This issue focuses on donor characteristics as well.

19 Kirk R, Dipchand AI, Davies RR, et al. ISHLT consensus statement on donor organ acceptability and management in pediatric heart transplantation. J Heart Lung Transplant 2020;39(4):331–41. doi: https://doi.org/10.1016/j.healun.2020.01.1345. Epub 2020 Jan 31. PMID: 32088108. An important statement setting forth donor organ acceptability and management, including ABO-incompatible transplants and defining acceptable titer levels. ABO-incompatible transplants have comparable survival data despite the patient population being in general younger and more ill.

23 Kozik D, Sparks J, Trivedi J et al. ABO-incompatible heart transplant in infants: a UNOS database review. Ann Thorac Surg 2020:S0003–4975(20)31422–3. doi: 10.1016/j.athoracsur.2020.06.073. Epub ahead of print. PMID: 32888926. A recent study of outcomes for ABO-incompatible infant heart transplants demonstrating excellent survival similar to ABO-compatible transplants.

62 Schure AY, Kussman BD. Pediatric heart transplantation: demographics, outcomes, and anesthetic implications. Paediatr Anaesth 2011;21:594–603. A review of the perioperative issues of relevance to all anesthesiologists who care for children with transplanted hearts.

63 Schumacher KR, Gajarski RJ. Postoperative care of the transplanted patient. Curr Cardiol Rev 2011;7:110–22. An excellent review of the

perioperative management of pediatric heart transplant recipients with particular emphasis on the early postoperative period.

130 Dickinson KM, Collaco JM. Cystic fibrosis. Pediatr Rev 2021;42:55–67. A well-written contemporary review that presents the remarkable medical therapy improvements for cystic fibrosis, including the medications that enhance cystic fibrosis transmembrane conductance regulator function, and other advances, that have dramatically reduced the early incidence of end-stage lung disease, and resulted in a dramatic decrease in pediatric lung transplants for this disease.

134 Grady RM. Beyond transplant: roles of atrial septostomy and Potts shunt in pediatric pulmonary hypertension. Pediatr Pulmonol 2021;56:656–60. An interesting review of an old surgery, the Potts shunt, to improve symptomatology, and duration of life, in severe pulmonary hypertension in children, which in turn reduces the need for lung transplantation in some patients in this population.

168 Suzuki Y, Cantu E, Christie J. Primary graft dysfunction. Semin Respir Crit Care Med 2013;34:305–19. An excellent and thorough contemporary review of the pathogenesis and treatment of PGD after lung transplantation.

183 Hayes D, Harhay MO, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society of Heart and Lung Transplantation: Twenty-fourth Pediatric Lung Tranplantation Report – 2021; Focus on Recipient Characteristics. J Heart Lung Transplant 2021; epub ahead of print. The most recent of the annual reports that updates worldwide pediatric lung transplants; this report focuses on recipient characteristics and risk factors for early and late deaths. 12-month survival has increased slightly to 86%, and 5-year survival, conditioned on 1-year survival, is about 60% for pediatric lung transplantation.

184 Bharat A, Querrey M, Markov NS, et al. Lung transplantation for patients with severe COVID-19. Sci Transl Med 2020;12(574): eabe4282. A case series from a team with one of the largest experiences with lung transplantation for COVD-19 pulmonary fibrosis.

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CHAPTER 33
Anesthesia for Pulmonary Hypertension

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Incidence, anatomy, natural history

Definition

Pulmonary hypertension (PH) has many different etiologies, in which all share the final common path of elevated pulmonary arterial pressure (PAP). After birth, PAP falls, reaching adult levels within a few months. In normal, healthy individuals, mean pulmonary artery pressure (mPAP) at rest is around 15 mmHg and is independent of age, ethnicity, and gender. During exercise, mPAP increases and is dependent on the level of exertion and age. During mild exercise, mPAP is 20 ± 5 mmHg in subjects under age 50 years compared to 30 ± 5 mmHg in subjects older than age 50 years, which makes it difficult to define normal mPAP during exercise, and hence, the definition of PH uses mPAP at rest [1]. Initially, PH was arbitrarily defined as an mPAP > 25 mmHg. However, this definition has recently changed, as two standard deviations above a normal mPAP of 15 mmHg would suggest an mPAP > 20 mmHg as the upper limit of normal (above the 97.5th percentile). However, this abnormal elevation of mPAP is not sufficient to define pulmonary vascular disease, as it can be due to an increase in cardiac output or pulmonary arterial wedge pressure. Therefore, the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 proposed to include pulmonary vascular resistance (PVR) ≥3 Wood Units (WU) in the definition of all forms of precapillary PH associated with an mPAP > 20 mmHg [2]. The current hemodynamic definitions of PH are shown in Table 33.1. The Pediatric Task Force of the sixth WSPH has chosen to follow this new adult definition of PH to maintain a common universal language and to facilitate transition from pediatric to adult care. This Pediatric Task Force further reinforced the need to index PVR to body surface area in children [3]. PVR index (PVRI) relates the absolute value of PVR to the patient's body surface area to account for the effect of body size on blood flow and it should be reported as WU m^2 [4]. An mPAP > 20 mmHg does not carry any implication of the presence or absence of pulmonary hypertensive vascular disease. PVR is important in the diagnosis and management of pulmonary hypertensive vascular disease in patients with congenital heart disease (CHD). PH complicates the course of many children and adults with CHD. The increase in PAP associated with CHD is secondary to either increased "precapillary" pulmonary blood flow (left-to-right shunt lesion) or increased postcapillary pressures (left heart disease). Based on the hemodynamic definition of PH (mPAP > 20 mmHg), almost all patients with a large unrestricted left-to-right shunt will have PH. What is important in this setting is the degree of pulmonary hypertensive vascular disease resulting in an increase in PVR. A patient with a high pulmonary blood flow and low PVR will have PH but can be safely treated with the closure of the shunt. On the contrary, a patient with low pulmonary blood flow, shunt reversal (right to left), cyanosis, and high PVR, the so-called Eisenmenger syndrome, will be harmed with shunt closure due to worsening right heart failure, as there is no longer a "pop-off" for blood flow [5]. Eisenmenger syndrome is an end stage, and usually irreversible, because of PH with a PVRI > 10 WU m^2 with reversed or bidirectional shunting of blood at an aortopulmonary, ventricular, or atrial level. However, between these two

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Table 33.1 Hemodynamic definitions of pulmonary hypertension (PH)

Definitions	Characteristics	Clinical groups[a]
Precapillary PH	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR≥ 3 WU	1, 3, 4, and 5
Isolated postcapillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR < 3 WU	2 and 5
Combined pre- and postcapillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR≥ 3 WU	2 and 5

Source: Simonneau et al. [2]. Reproduced with permission of European Respiratory Society.
mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; WU, Wood Units.
[a] Clinical groups – see Table 33.2.

extremes of PH and associated CHD is a challenging gray zone that requires careful diagnostic evaluation to guide future management.

Classification

Since inception in 1973, the World Health Organization (WHO) group classification system for PH has provided researchers and clinicians an evolving framework from which to investigate, diagnose, and treat patients with a diverse collection of pulmonary vascular diseases [2, 6]. The clinical classification of PH has five categories based on shared pathological mechanisms, hemodynamic characteristics, and management strategies (Table 33.2). Subsequent iterations of this clinical classification have maintained a comparable structure with changes paralleling scientific advancement. The definitions are accepted worldwide and used daily in practice by clinicians as inclusion/exclusion criteria for clinical research and in the labeling of new therapeutics for the treatment of PH.

The WHO groups 1–5 classification system for children is problematic, as it does not reflect the complex heterogeneity of factors that contribute to pediatric PH. As a result, the Pulmonary Vascular Research Institute Pediatric Taskforce proposed a new classification of pediatric PH at its meeting in Panama in 2011 [7]. The classification has 10 categories based on clinical pediatric practice and reflects the heterogeneous nature of pediatric PH (Table 33.6). The Panama classification includes an additional definition of PH for children with univentricular circulations: following a cavopulmonary anastomosis, PH is defined as a PVRI≥ 3 WU m^2 or a transpulmonary gradient (mPAP – left atrial pressure) >6 mmHg even if the mPAP is <20 mmHg (Box 33.1) [7, 8]. In this setting of nonpulsatile blood flow to the pulmonary arteries, even though mPAP may not be greater than 20 mmHg, significant pulmonary hypertensive vascular disease can lead to a poor outcome. With the agreement of the Pediatric Taskforce, some of these items were included in the most recent 2018 Pulmonary Hypertension Classification to have a more comprehensive classification, inclusive of both adults and children [9].

Children with CHD and PH are in group 1, pulmonary arterial hypertension (PAH). Group 1.4.4 PAH includes patients with simple operable and inoperable CHD, subgrouped as those with Eisenmenger physiology, those with PAH and left-to-right shunts, those with PAH thought to be incidental to their CHD, and those with postoperative defects. Transient PH following repair of CHD occurs in 21.9 cases per million and is one of the commonest forms of PAH in children, second only to persistent PH of the newborn [10]. Complex heart diseases have been assigned to group 5.4.

Group 2, PH due to left heart disease, includes congenital and acquired left heart inflow and outflow tract obstruction, such as pulmonary vein stenosis, cor triatriatum, mitral stenosis, and cardiomyopathies. This group causes the "postcapillary" increase in PAP. In group 3, PH due to lung disease and/or hypoxia, developmental lung diseases are emphasized due to the important role of abnormal lung vascular growth in the pathogenesis of PH. Examples include congenital diaphragmatic hernia, bronchopulmonary dysplasia (BPD), alveolar capillary dysplasia, and surfactant protein abnormalities. Group 4, PH due to pulmonary artery obstructions, and group 5, PH with unclear and/or multifactorial mechanisms, including complex CHD, are rare causes of pediatric PH.

The characterization of PH according to these classifications is an essential part of the diagnostic workup of PH. The treatment strategy and prognosis of pediatric PH largely depend on its subclass and associated conditions. It is, therefore, important to correctly characterize the type of PH using standardized diagnostic workup (Figure 33.1). However, in pediatric PH, there is often more than one associated condition identified, which leaves it to the clinician to determine the contribution of each condition to the PH and to decide on which condition therapy should be focused. However, there is now a shift away from this historic classification paradigm to a genotype–phenotype model, which potentially removes the boundaries between the current groups [11]. The guidelines for the diagnosis and management of pediatric and adult PH have comparable themes, but recommendations for treatment in children are based largely on expert consensus and extrapolation from adult data [12]. Identifying parallels in the genotype–phenotype profile among adult and pediatric patients with comparable genetic mutations may simplify investigation and treatment. Armed with specific knowledge about genotype–phenotype of their patient, clinicians may be better equipped to provide precision care regardless of patient age. The large-scale PVDOMICS study (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) is utilizing the principle of phenomics (e.g. genomics, transcriptomics, proteomics, metabolomics) to create a rich data resource from which to redefine PH classification at the molecular level [13, 14].

Epidemiology

The major etiologies of pediatric PH cases are idiopathic PAH (IPAH), heritable PAH (HPAH), and PAH associated with CHD (PAH-CHD). Gene mutations involved in the transforming growth factor-β (TGF-β) signaling pathway, primarily within bone morphogenetic protein receptor type-2 (BMPR-2), have been shown to be important in IPAH

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Table 33.2 Updated clinical classification of pulmonary hypertension

1. PAH
   - 1.1. Idiopathic PAH
   - 1.2. Heritable PAH
   - 1.3. Drug and toxin induced PAH (Table 33.3)
   - 1.4. PAH associated with:
     - 1.4.1. Connective tissue disease
     - 1.4.2. HIV infection
     - 1.4.3. Portal hypertension
     - 1.4.4. Congenital heart disease
     - 1.4.5. Schistosomiasis
   - 1.5. PAH long-term responders to calcium channel blockers (Table 33.4)
   - 1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement (Table 33.5)
   - 1.7. Persistent pulmonary hypertension of the newborn (PPHN)
2. PH due to left heart disease
   - 2.1. PH due to heart failure with preserved LVEF
   - 2.2. PH due to heart failure with reduced LVEF
   - 2.3. Valvular heart disease
   - 2.4. Congenital/acquired cardiovascular conditions leading to postcapillary PH
3. PH due to lung diseases and/or hypoxia
   - 3.1. Obstructive lung disease
   - 3.2. Restrictive lung disease
   - 3.3. Other lung disease with mixed restrictive/obstructive pattern
   - 3.4. Hypoxia without lung disease
   - 3.5. Developmental lung disorders
4. PH due to pulmonary artery obstructions
   - 4.1. Chronic thromboembolic PH
   - 4.2. Other pulmonary artery obstructions
     - 4.2.1. Sarcoma (high or intermediate grade) or angiosarcoma
     - 4.2.2. Other malignant tumors:
       - Renal carcinoma
       - Uterine carcinoma
       - Germ cell tumors of the testis
       - Other tumors
     - 4.2.3. Nonmalignant tumors
       - Uterine leiomyoma
     - 4.2.4. Arteritis without connective tissue disease
     - 4.2.5. Congenital pulmonary artery stenosis
     - 4.2.6. Parasites
       - Hydatidosis
5. PH with unclear and/or multifactorial mechanisms
   - 5.1. Hematologic disorders
     - Chronic hemolytic anemia
     - Myeloproliferative disorders
   - 5.2. Systemic disorders and metabolic disorders
     - Pulmonary Langerhans cell histiocytosis
     - Gaucher disease
     - Glycogen storage disease
     - Neurofibromatosis
     - Sarcoidosis
   - 5.3. Others
     - Chronic renal failure with or without hemodialysis
     - Fibrosing mediastinitis
   - 5.4. Complex congenital heart disease

Source: Adapted from Simonneau et al. [2].

LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension, PCH: pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease.

Table 33.3 Updated classification of drugs and toxins associated with PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-Tryptophan
Benfluorex	St. John's wort
Methamphetamines	Amphetamines
Dasatinib	Interferon α and β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide
	Indirubin (Chinese herb Qing-Dai)

Source: Simonneau et al. [2]. Reproduced with permission of European Respiratory Society.

Table 33.4 Definitions of acute and long-term response

Acute pulmonary vasoreactivity[a] for patients with idiopathic, hereditable, or drug-induced PAH	Reduction in mPAP ≥ 10 mmHg to reach an absolute value of mPAP ≤ 40 mmHg. Increased or unchanged cardiac output
Long-term response to CCBs	NYHA Functional Class I/II With sustained hemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only

Source: Simonneau et al. [2]. Reproduced with permission of European Respiratory Society.
CCB, calcium channel blocker; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.
[a] Nitric oxide (10–20 ppm) is recommended for performing vasoreactivity testing, but IV epoprostenol, IV adenosine, or inhaled iloprost can be used as alternatives.

Table 33.5 Signs evocative of venous and capillary (pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis) involvement

Pulmonary function tests	Decreased D_{LCO} (frequently <50%) Severe hypoxemia
Chest high-resolution CT	Centrilobular ground-glass opacities/ nodules Mediastinal lymph node enlargement
Response to PAH therapy	Possible pulmonary edema
Genetic background	Biallelic EIF2AK4 mutations
Occupational exposure	Organic solvent (trichloroethylene)

Source: Simonneau et al. [2]. Reproduced with permission of European Respiratory Society.
DLCO, diffusing capacity of the lung for carbon monoxide; PAH, pulmonary arterial hypertension.

and HPAH. There are other mutations, which are also thought to be important in the pathogenesis of PAH, including activin-like kinase-1 (ALK-1), T-box 4, SOX17, and endoglin mutations [15, 16]. BMPR-2 is the most common gene mutation associated with pediatric PAH and can be identified in 10–20% of pediatric patients with IPAH/HPAH [10, 17, 18].

Table 33.6 The Panama classification: 10 categories of pediatric pulmonary hypertensive vascular disease

Category	Description
1	Prenatal or developmental pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaption
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders

Source: Cerro et al. [7]. Reproduced with permission of John Wiley & Sons.

Box 33.1: The modern definition of pulmonary arterial hypertension in children with biventricular and palliated univentricular circulations.

mPAP = mean pulmonary artery pressure
PVRI = pulmonary vascular resistance index
CO = cardiac output
TPG = transpulmonary gradient

Biventricular circulation

mPAP > 20 mmHg and PVRI ≥ 3 Wood Units m^2
Sitbon criteria for positive acute vasodilator response defined as a decrease in mPAP by at least 10 mmHg to a value of <40 mmHg with sustained cardiac output [62]

Univentricular circulation

Following palliation with a cavopulmonary anastomosis
PVRI ≥ 3 Wood Units m^2 or TPG > 6 mmHg EVEN IF mPAP < 20 mmHg

Two large registries have provided further insights into the etiology of pediatric PH. The Tracking Outcomes and Practice in Pediatric (TOPP) PH registry reported 362 patients with confirmed PH [19]. Of these patients, 317 (88%) had PAH, of which 57% were characterized as IPAH or HPAH and 36% as PAH-CHD. Only three patients had chronic thromboembolic PH. Chromosomal anomalies, mainly trisomy 21, or syndromes were reported in 47 (13%) of the patients. Another large registry for pediatric PH is from the Netherlands. This registry reports 2,845 (87%) of 3,263 pediatric patients with PAH in group 1 of the PH classification, including transient PAH (82%) or progressive PAH (5%) [10]. The most common cause of transient PAH was Persistent Pulmonary Hypertension of the Newborn (PPHN) (58%), and the most common cause of progressive PAH was PAH-CHD (72%). Trisomy 21 was the most frequent chromosomal abnormality (12%), a rate similar to that observed in the TOPP registry.

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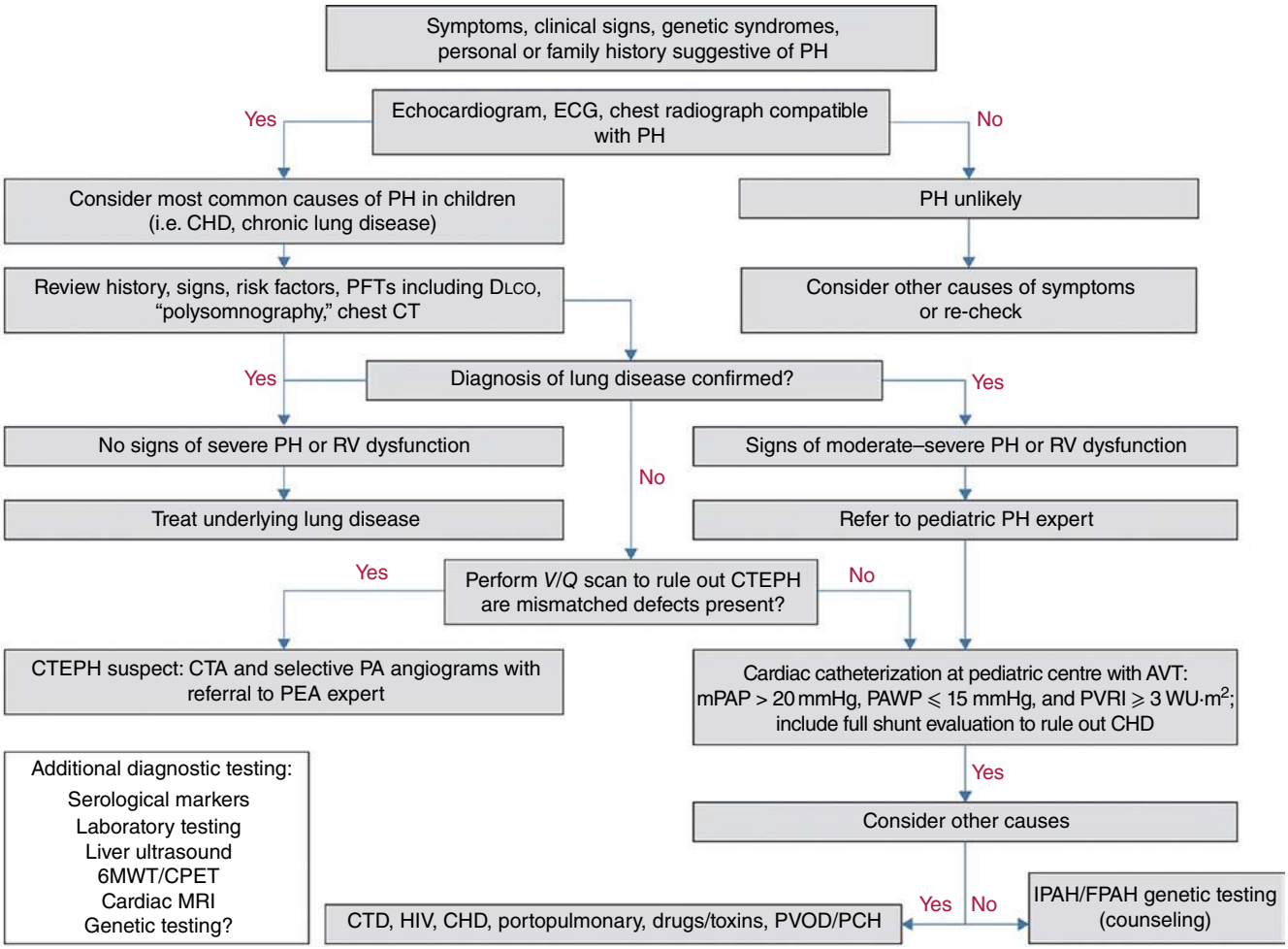


Figure 33.1 Diagnostic algorithm for pulmonary hypertension (PH) in children. 6MWT, 6-minutes walk test; AVT, acute vasodilator testing; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CT, computed tomography; CTA, CT angiography; CTD, connective tissue disease; CTEPH, chronic thromboembolic PH; DLCO, diffusing capacity of the lung for carbon monoxide; IPAH/FPAH, idiopathic/familial pulmonary arterial hypertension, mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; PA, pulmonary artery; PAWP, pulmonary arterial wedge pressure; PCH, pulmonary capillary haemangiomatosis; PEA, pulmonary endarterectomy; PFT, pulmonary function test; PVOD, pulmonary veno-occlusive disease; PVRI, pulmonary vascular resistance index; RV, right ventricular; V/Q, ventilation/perfusion; WU, Wood Units. (Source: Rosenzweig et al. [3]. Reproduced with permission of European Respiratory Society.)

PH is a rare disease. The incidence and prevalence of PH in the pediatric population are not well known. In the Netherlands' registry, the annual incidence of IPAH and PAH-CHD were 0.7 and 2.2 cases/million, respectively. The prevalence of PAH-CHD was 15.6 cases/million [10]. The national registry from the United Kingdom reports similar numbers with an annual incidence of IPAH of 0.48 cases/million children and a prevalence of 2.1 cases/million [20]. In a multicenter study in France, the estimated prevalence of PAH was 3.7 cases/million children, with IPAH (60%) and PAH-CHD (24%) being the main etiologies [21].

Survival for patients with PH has improved with the introduction of management guidelines, dedicated centers, and new drug therapies. Before targeted drug therapies were available for PH, the estimated median survival of children and adults with IPAH were similar, 4.12 and 3.12 years, respectively [22]. After the introduction of targeted pulmonary vasodilators, the survival rate for children with PAH has continued to improve. In the combined pediatric and adult US REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry, patients with childhood onset PAH had 1-, 3-, and 5-year survival rates of 96, 84, and 74%, respectively [23]. There was no significant difference in 5-year survival between IPAH/HPAH (75%) and PAH-CHD (71%). Similar data have been published from studies in the Netherlands and United Kingdom [20, 24, 25]. Although overall survival has improved, patients with repaired CHD and pulmonary hypertensive vascular disease have a high mortality risk.

Pathophysiology of pulmonary hypertension in congenital heart disease

PH associated with CHD is classified in group 1, PAH. This group distinguishes itself from the other four categories by its characteristic pattern of vascular remodeling, progressive

nature, and response to specific medical therapy. Heath and Edwards published the first description of pulmonary vascular remodeling due to CHD in 1958 [26]. They divided the histological progression from grades 1 to 6 in increasing severity. Later, Rabinovitch developed the morphometric approach, which quantifies the thickness of the pulmonary arterial muscle, the degree of abnormal distal extension of smooth muscle, and the density of small pulmonary arteries relative to the number of alveoli [27]. The morphometric structural findings are graded from A through C in increasing severity of changes. This morphometric analysis has contributed to our understanding of pulmonary vascular remodeling by establishing that abnormal extension of smooth muscle and a reduction of small artery density are a hallmark of pulmonary hypertensive vascular disease. This approach has emphasized that early age to correct congenital heart defects helps preserve small pulmonary arteries and predicts good pulmonary hemodynamics postoperatively. The pulmonary vascular remodeling that is characteristic for PAH involves adventitial thickening, medial hypertrophy, and intimal proliferation, including the formation of plexiform lesions [28]. This vascular remodeling leads to arterial wall thickening and occlusion of small distal pulmonary arteries. Together with other mechanisms including vasoconstriction, inflammation, and thrombosis, the vascular wall thickening and occlusion will consequently increase PAP and PVR (Figure 33.2) [29]. This increase in right ventricular (RV) afterload increases RV workload, eventually resulting in RV failure.

The pulmonary vascular bed plays a key role in the presentation and management of children with almost all forms of CHD. Four variables are important in the development of pulmonary hypertensive vascular disease and whether it will regress or progress after repair of a congenital cardiac shunt lesion:

1. The age of the patient at repair
2. The type of cardiac lesion
3. The PVRI at operation
4. Individual genetic and environment factors and comorbidities

The evolution of PAH-CHD and the age at which it presents itself depends on the type of shunt lesion. In patients with a shunt at the pretricuspid valve level (e.g. ASD), there is an increased pulmonary volume load with a normal pressure load. Only 5–20% of these patients will develop severe PAH, and usually not until the third or fourth decade of life [30, 31]. In patients with nonrestrictive shunts at the posttricuspid valve level, the increased pulmonary volume is accompanied by an increased pressure load due to pressure equalization across the shunt defect. In these patients, PAH usually develops more rapidly during the first few years of life. If left uncorrected, these systemic to pulmonary shunts will result in steadily increasing PVR, and when this exceeds the systemic vascular resistance (SVR), the shunt will reverse resulting in hypoxemia and cyanosis, which are the hallmarks of Eisenmenger syndrome [5]. For this reason, most CHD shunt lesions should be repaired within the first 2 years of life. The exact level of PVRI that precludes safe closure of a defect is often debated and varies with each lesion. The WSPH proposed criteria for shunt closure in patients with net left-to-right shunting (Table 33.7) [32]. Complex congenital heart defects, such as transposition of the great arteries, truncus arteriosus, and aortopulmonary window, present with pulmonary hypertensive vascular disease much earlier and should, therefore, be repaired in the first weeks of life.

Patient genetic and environmental factors may influence the timing of repair of congenital heart defects with PAH. Pediatric PAH occurs in 20–40% of children with genetic disorders, including trisomy 21, Noonan, Velocardiofacial, and Jacobsen syndromes [18]. Furthermore, many children with PAH have clinical signs of a syndrome, such as dysmorphic features, which cannot be explained by a known syndrome diagnosis or genetic test. The frequent occurrence of genetic abnormalities in children with PAH suggests the existence of still unknown genetic pathways involved in the disease process of PAH. The BMPR-2 mutation has been described in 6% of children with CHD [33]. Comorbidities may also exacerbate PAH-CHD. For example, children with trisomy 21 are at higher risk of developing PH due to sleep-disordered breathing, upper airway obstruction, silent aspiration with recurrent pneumonias, and pulmonary hypoplasia [34]. The net result is episodes of hypoxia, which in turn may exacerbate the pulmonary vascular disease from CHD. In developing countries, there may be additional comorbidities to consider. In Africa, in a cohort of children with CHD, 53% were anemic, 47% underweight, and 33% had marasmus compared to a control group without CHD, of whom none had marasmus and only 14% were underweight [35]. Tuberculosis is twice as common in patients with CHD, especially in those with lesions with an increased pulmonary blood flow, and if treatment is available, the major cause of morbidity is delay of cardiac surgery [36]. Unfortunately, tuberculosis may mask the signs of CHD and result in a delay in diagnosis of CHD and subsequent surgical repair. Human immunodeficiency virus (HIV) infection is endemic in sub-Saharan Africa. In Uganda, CHD affects 5% of children with HIV compared to 3% in developed countries [37]. More recently, coronavirus disease 2019 (COVID-19) has had a catastrophic impact on global health. The virus responsible for the pandemic is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the most frequently reported comorbidities in children who become critically ill with the virus are chronic lung disease, obesity, neurodevelopmental disabilities, and CHD. Patients with PH are vulnerable to SARS-CoV-2, as it is a respiratory virus that causes PH via multiple pathways including lung inflammation and fibrosis, vasoconstriction, and thrombosis [38].

Environmental factors may also influence the timing of surgical repair of congenital heart defects. High altitude has effects on normal neonatal pulmonary vascular transition that is related not only to altitude but also to ancestry. Ethnic groups with recent migration to high altitude have lower oxygen saturations and higher PAP than those with a long ancestry of high altitude living, such as native residents of the Andes mountain range and Tibet. In addition, the incidence of CHD increases at higher altitude, the ductus arteriosus is larger, and its closure delayed, with a higher pulmonary to systemic blood flow ratio for a given PVR. As a result, management decisions, particularly the timing of surgical repair, are different at high altitude [39, 40].

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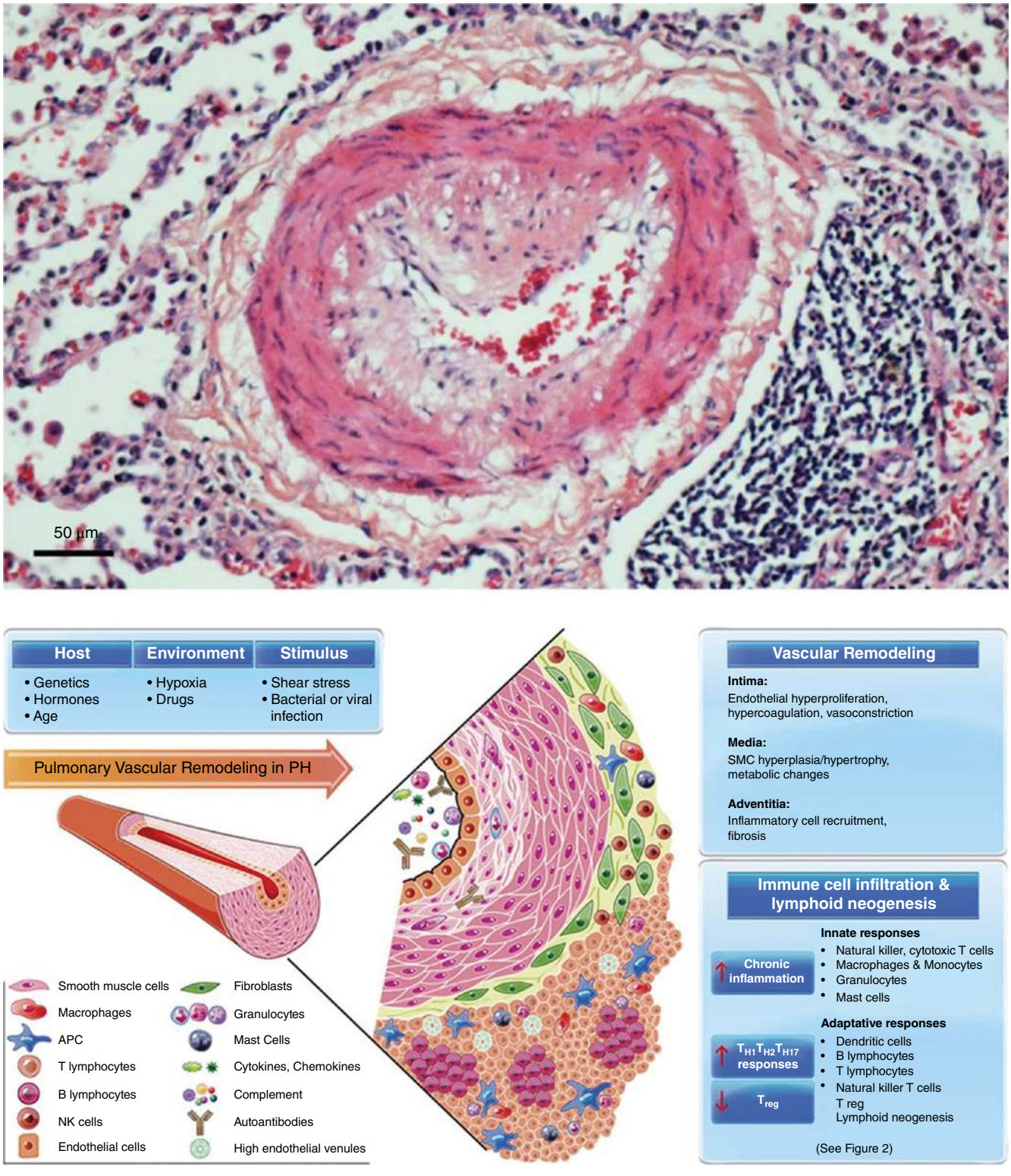


Figure 33.2 Pulmonary vascular changes in pulmonary arterial hypertension includes infiltrating adaptive and innate immune cells. In the top panel is a representative histopathology of a vessel with severe neointimal formation represented below by a diagrammatic illustration. The histopathology shows a single endothelial layer and an eccentric neointima (pale pink) that contains cells that have markers of inflammatory cells and others that stain with markers of smooth muscle but appear poorly differentiated. The medial muscular layer is expanded, and there is an abundant adventitial layer. This vessel is decorated with complement and autoantibodies, infiltrated by neutrophils in the lumen attacking the vessel wall and other inflammatory cells binding to the endothelium and infiltrating. The neointima is composed of pale cells and matrix and infiltrating T and B cells, and in the adventitia, there are dendritic cells, macrophages, and mast cells, and in the periadventitial space tertiary lymphoid follicles characterized by T cells, B cells, and plasmacytoid dendritic cells (APC). NK indicates natural killer; PH, pulmonary hypertension; and SMC, smooth muscle cell. (Source: Rabinovitch et al. [29]. Reproduced with permission of Wolters Kluwer Health, Inc.)

KEY POINTS: CLASSIFICATION AND DEFINITION OF PH

- The current definition of PH is an mPAP > 20 mmHg at rest, as measured by right heart catheterization. However, this abnormal elevation of mPAP in isolation is not sufficient to define pulmonary vascular disease, as it can be due to an increase in cardiac output or pulmonary artery occlusion pressure (PAOP).
- Hemodynamic definitions of PH include precapillary, isolated postcapillary, or a combination of both.
- The clinical classification of PH is divided into five groups.
- There are additional definitions of PH in children, including those with single ventricle physiology.
- Evolving definitions of PH utilize the principles of phenomics (genomics, transcriptomics, proteomics, and metabolomics) to redefine PH at the molecular level.

Table 33.7 Guidance for assessing operability in pulmonary arterial hypertension associated with congenital heart disease

PVRI wood units (m^2)	PVR wood units	Correctability/favorable long-term outcome
<4	<2.3	Yes
>8	>4.6	No
4–8	2.3–4.6	Individual patient evaluation in tertiary center

Source: Rosenzweig et al. [3]. Reproduced with permission of European Respiratory Society.
Special considerations include age of patient, type of defect, and comorbidities, resting or exercise-induced desaturation is a concern and PAH therapy (treat with intent-to-repair approach has not been proven).

Assessment of pulmonary hypertension

The clinical assessment of the child with PAH and CHD is aimed at differentiating those with reversible pulmonary vascular disease who are operable from those with irreversible or fixed disease. In cases that are not straightforward, it is important to put together all the clinical information without relying on one single parameter. The clinical presentation of pediatric PH is nonspecific and age-dependent. The most common presenting symptom is reduced exercise capacity accompanied by fatigue and dyspnea. Young infants may present with feeding problems and failure to thrive. Other presenting symptoms include cyanosis, cough, and chest or abdominal pain. Syncope as a presenting symptom is specific to pediatric PH and is reported in 25–30% of children with PH and is most frequent in patients without a shunt defect [18–20]. There is often a long delay between the onset of symptoms and diagnosis due to the low specificity of presenting symptoms and the rarity of the disease. Screening should take place for children belonging to high-risk groups based on underlying conditions of family members with PH.

The functional status of children and adults with PH, with respect to exercise capacity and symptoms, can be classified using the WHO Functional Classification (WHO-FC) [41]. The WHO-FC scale is based on the New York Heart Association (NYHA) classification, which evaluates symptoms including limitation of physical activity, dyspnea, fatigue, chest pain, and right heart failure. Although the WHO functional class is not designed specifically for children, it has been shown to correlate with 6-minute walk distance and hemodynamic parameters [21, 23, 24, 42]. Another scale has been developed for children, the age-adjusted Panama Functional Classification (Panama-FC) [43]. In children, both the WHO-FC and Panama-FC scales have been shown to correlate well with PH disease progression. The Panama-FC appears to be better for long-term follow-up, while the WHO-FC appears to be better for short-term monitoring, for example, after changes to treatment [44].

After a thorough history and physical examination of the patient, blood should be drawn for laboratory analysis including complete blood count, metabolic panel, coagulation profile, and biomarkers of PH. Biomarkers that specifically indicate the pathologic mechanism, the severity of the disease, and the treatment response would be ideal tools for the management of PH, but they are still the subjects of research. Anemia, hypocarbia, elevated uric acid, and C-reactive protein levels are nonspecific markers of disease severity. Brain natriuretic peptide (BNP) and N-terminal fragment of pro-BNP, which reflect the degree of atrial stretch and heart failure, are recommended for disease monitoring [45].

Noninvasive imaging for the assessment of PH includes chest X-ray, echocardiography, CT scan of the lungs, nuclear medicine ventilation perfusion scan, and magnetic resonance imaging (MRI) [46]. By the time the diagnosis of PH is made, 90% of patients have an abnormal chest X-ray, although sensitivity and specificity are low [47]. Typical features on chest X-ray include elevated cardiac apex due to RV hypertrophy, enlarged right atrium, prominent pulmonary outflow tract, enlarged pulmonary arteries, and pruning of peripheral pulmonary arteries.

Echocardiography provides information about the anatomic details of the lesion, assessment of shunt direction, and estimates of pulmonary artery pressures (PAPs) [48]. Echocardiography may support the diagnosis of PH with qualitative images of elevated RV pressure, such as RV hypertrophy and septal wall flattening. Quantitative information may be obtained on echocardiography if there is tricuspid regurgitation during systole (Figure 33.3). In this case, the modified Bernoulli equation may be applied to estimate PAP with a tricuspid regurgitant velocity of greater than 2.8 m/s being highly indicative of PH (Box 33.2) [1, 49]. Measurement of the end-systolic RV to left ventricular (LV) diameter ratio correlates with invasive measurements of the severity of PH [50]. Echocardiography can provide information on the direction of flow through a shunt. A pure left-to-right shunt across a defect indicates that the PVR is lower than the SVR. The presence of reversed or bidirectional flow across an ASD, PDA, or VSD is concerning and suggests the need for cardiac catheterization and acute vasoreactivity testing. Transthoracic echocardiography is an attractive method to assess children with PH and possibly enable the cardiologists to lengthen the interval between cardiac

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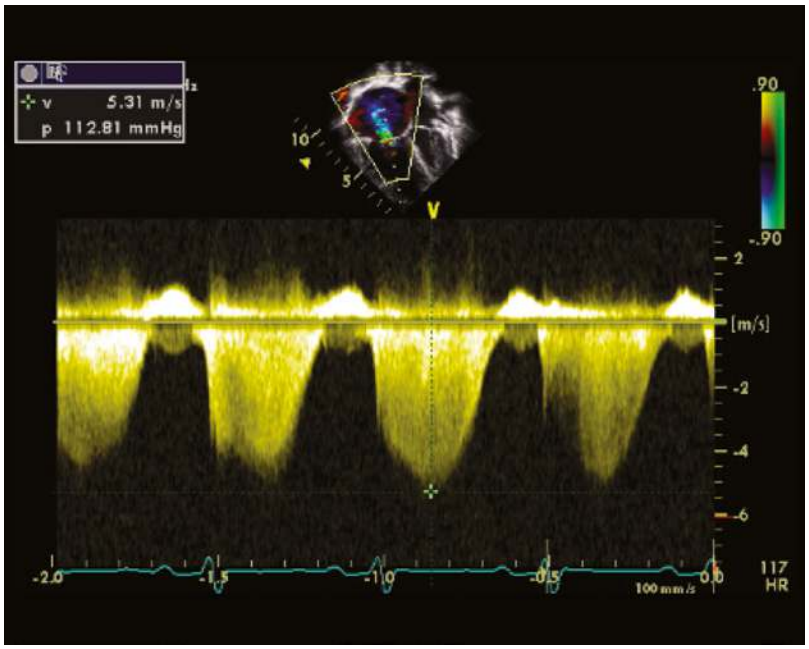


Figure 33.3 Echocardiographic image showing Doppler of tricuspid regurgitant jet used to estimate pulmonary artery pressure. (Source: Figure supplied by Dr. Mark Twite and Dr. Robert Friesen.)

Box 33.2: Estimating PAP from systolic tricuspid regurgitant jet velocity on echocardiography

sPAP = systolic pulmonary artery pressure
RAP = right atrial pressure
mPAP = mean pulmonary artery pressure

Modified Bernoulli equation:

$$\text{sPAP} = 4v^2 + \text{RAP}$$

e.g. $\text{sPAP} = 4\left(2.8^2\right) + 10 = 41\ \text{mmHg}$

Converting sPAP to mPAP

$$\text{mPAP} = (0.61 \times \text{sPAP}) + 2\ \text{mmHg}$$

e.g. $\text{mPAP} = (0.61 \times 41) + 2 = 27\ \text{mmHg}$

v = tricuspid regurgitation velocity using Doppler echocardiography

catheterizations required to monitor ongoing therapy. There are many echocardiographic techniques in the research and validation phase. One technique is to monitor the RV systolic to diastolic duration ratio, in which an increase has been shown to be associated with worse RV function, exercise capability, and survival [51]. Another technique using echocardiography is to measure the degree of tricuspid annular plane systolic excursion (TAPSE), which has been shown to reflect RV function and prognosis in PH [52, 53].

MRI is being increasingly used to evaluate patients with PH. MRI allows high spatial resolution of the intracardiac structures and vasculature involved in PH pathophysiology (Figure 33.4). MRI is not constrained by body habitus and patients with poor acoustic windows and surgical scars. The unusual geometry of the RV does not preclude accurate measurements of RV volume and ejection fraction (EF). Advances in MRI have allowed detailed assessment of flow through the heart and vasculature and reflect vascular hemodynamics and vascular remodeling. Techniques such as four-dimensional flow MRI (4D-Flow MRI) provide blood velocity data in all spatial directions, which allows for flow analysis of complex hemodynamic patterns [54, 55]. An example of how this technology may be applied is shown in Figure 33.5. MRI is a promising tool to comprehensively describe the entire RV–PA axis and the involvement of the left heart. Machine learning approaches to improve automation and accuracy of MRI metrics and identify imaging features of PH are an area of active research with promising clinical utility [46, 56, 57]. The combination of MRI and direct PAP measurement via a catheter may provide more information than either test alone.

Despite advances in noninvasive imaging techniques, cardiac catheterization with vasodilator testing is necessary for diagnosis, treatment stratification, and prognosis of PH in children [58]. There are three objectives during the catheterization procedure: to obtain hemodynamic data, to test vasoreactivity, and to rule out any associated disease states. Accurate hemodynamic data are essential for the diagnosis and ongoing monitoring of patients with PH. End hole or flow-directed catheters are used to obtain hemodynamic data. Catheters with multiple side holes are used for angiography to prevent myocardial staining during injection. During catheterization, baseline measures include right atrial pressure, PAP, systemic arterial pressure, mixed venous and systemic arterial saturation, cardiac output, and PAOP. From these measures, important calculations can be made for pulmonary to systemic flow ratio ($Q_p : Q_s$) (Box 33.3) and PVR (Box 33.4) [59, 60]. It is essential that the anesthesiologist maintains stability during these periods of measurement and that the conditions under which they are made are clearly communicated. Most cardiac catheterization laboratories will

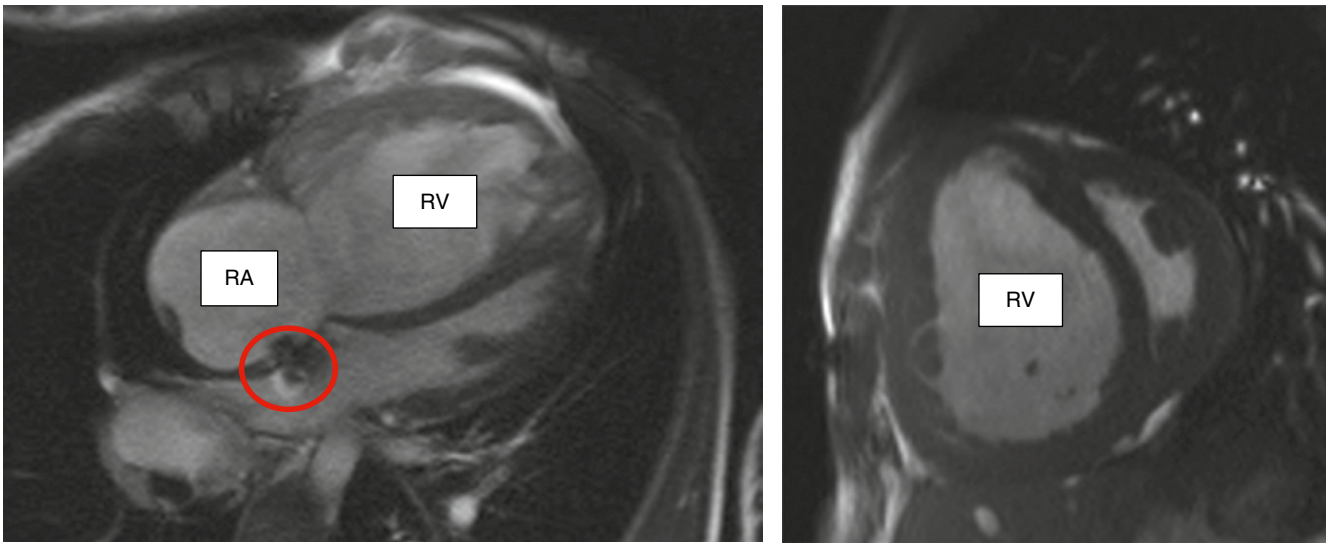


Figure 33.4 Still MRI cine images demonstrating features of pulmonary hypertension. Both images are from the same patient. Left image: this horizontal long long-axis, four four-chamber view of the heart demonstrates an enlarged right atrium (RA) and dilated right ventricle (RV). There is a stent placed in an atrial septostomy (red circle), with dephasing artifact showing bidirectional flow. Right image: this short short-axis, mid-ventricular view shows RV dilation and severe septal flattening and septal shift towards the left ventricle. (Source: Images courtesy of Dr. Richard Friesen.)

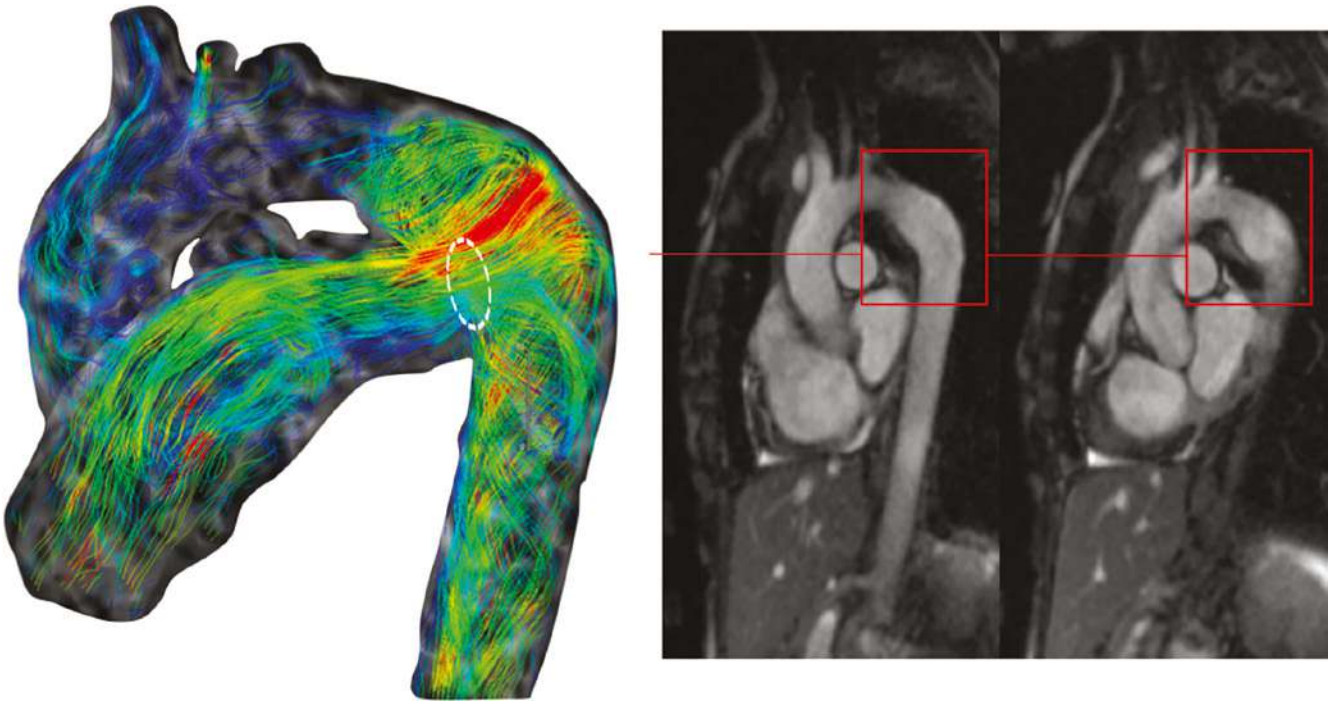


Figure 33.5 Four-dimensional flow magnetic resonance imaging (4D-Flow MRI) of a Potts shunt. Vortex formation is seen at the aortic entrance of the Potts shunt. In this region (red square), aneurysmal dilation of the aorta is demonstrated by bright blood imaging. Aneurysmal dilation in this situation has been postulated to be associated with abnormal flow hemodynamics creating localized pressure-–volume stress on the aortic wall. (Source: Schäfer et al. [55]. Reproduced with permission from John Wiley & Sons.)

obtain baseline measurements in room air, followed by 70–100% oxygen and then introduce an acute vasodilator such as inhaled nitric oxide (iNO) 20–40 parts per million (ppm). In a recent review of cardiac catheterization laboratory protocols and hemodynamic data in pediatric patients with PH, general anesthesia was found to decrease systemic arterial pressure, but there was no difference between general anesthesia and procedural sedation on mPAP or PVRI. It also demonstrated that pediatric patients with PH demonstrate a higher incidence of PH associated with CHD and neonatal-specific disorders compared to adults. The review also points out that pediatric PH had baseline mPAP < 40 mmHg but was

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Box 33.3: Calculating Q_p and Q_s

Q_p = pulmonary blood flow
Q_s = systemic blood flow
Sat Ao = aortic saturation
Sat MV = mixed venous saturation
Sat PV = pulmonary vein saturation
Sat PA = pulmonary artery saturation

Based on the Fick principle

$$Q_p : Q_s = \frac{\text{Sat Ao} - \text{Sat MV}}{\text{Sat PV} - \text{Sat PA}}$$

Box 33.4: Calculating PVR

PVR = pulmonary vascular resistance
PVRI = pulmonary vascular resistance index
P = pressure
Q_p = pulmonary blood flow
PAP = pulmonary artery pressure
LAP = left atrial pressure (equivalent to pulmonary artery occlusion pressure PAOP)

Based on Ohm's Law

$$\text{PVR} = \frac{P_{in} - P_{out}}{Q_p} = \frac{\text{Mean PAP} - \text{Mean LAP}}{Q_p}$$

$$\text{PVR is measured in Wood Units} = \text{mmHg / L / min}$$

$$\text{or } 80 \times \text{Woods units} = \text{dyne s / cm}^5 \text{ (metric units)}$$

$$\text{PVRI} = \text{PVR m}^2$$

>50% of their systemic blood pressure, illustrating the difficulty of applying adult criteria to children with PH [61].

The degree to which mPAP and PVR can be decreased acutely by the administration of fast-acting, short-duration vasodilators reflects the extent to which vascular smooth muscle constriction is contributing to the hypertensive state. The response to vasodilators has important therapeutic implications in PH, and almost all patients will undergo a vasodilator trial during their initial cardiac catheterization. Three separate situations may be evaluated with the acute vasodilator trial: potential treatment with calcium channel blockers (CCBs), assessment of operability in children with CHD, and determining prognosis. Inhaled nitric oxide at 10–80 ppm is the preferred selective pulmonary vasodilator, but intravenous epoprostenol, intravenous adenosine, or inhaled iloprost may be used as alternatives. However, optimal dosing in small children is not well defined for the latter drugs. The Sitbon criterion for a positive vasodilator response in adults is a reduction in mPAP by at least 10 mmHg, to a value of <40 mmHg, with sustained cardiac output [62]. The same Sitbon criteria are now used in children, as it has been shown that responders have a sustained benefit from CCB therapy [63]. It is estimated that 70–90% of children with severe PH are nonresponders to acute vasodilator testing and therefore require therapy other than calcium channel antagonists [8, 64]. In the cardiac catheterization lab, balloon occlusion of a shunt is the best means of demonstrating the short-term effect of shunt closure on PAP. It must be emphasized that cardiac catheterization of children with PH should be performed in experienced centers able to manage potential complications such as PH crisis requiring extracorporeal membrane oxygenation (ECMO) support [65, 66].

KEY POINTS: ASSESSMENT OF PH

- A comprehensive evaluation of patients with newly diagnosed PH is essential to determine management and prognosis.
- Cardiac catheterization with direct measurement of PAP, calculation of pulmonary vascular resistance and pulmonary vasoreactivity testing, is the gold standard for assessment. It is essential that the anesthesiologist maintains stability during these periods of measurement and that the conditions under which they are made are clearly communicated.
- Noninvasive techniques are used to monitor patients with PH including echocardiography and increasingly cardiac MRI.

Medical management of pulmonary hypertension

The factors leading to an increase in mPAP may all eventually result in increased PVR and pulmonary hypertensive vascular disease. As the pulmonary vasculature remodels in PH, there are changes that may be reactive or fixed. Reactive changes will result in vasodilation of the pulmonary vasculature to an exogenously administered pulmonary vasodilator such as iNO. Fixed changes are unreactive to such pulmonary vasodilators. As the disease processes leading to PH progress, the cross-sectional area of the pulmonary vasculature decreases according to Poiseuille's law leading to increased PVR. Poiseuille's law states that the resistance of a vessel is proportional to the fourth power of the radius. In other words, as the pulmonary arterioles develop thickening of their walls and a smaller intraluminal radius, the resistance will increase exponentially. A pulmonary hypertensive crisis is an acute on chronic increase in PVR during the perioperative period due to an acute increase in vascular tone of the reactive portion of the pulmonary vasculature. Early recognition and appropriate management of a pulmonary hypertensive crisis can be lifesaving.

The current treatment strategies for PH are aimed at three pathological processes. Vasodilators treat reactive vasoconstriction, antiproliferative drugs attenuate vascular remodeling, and anticoagulation may be used to treat and prevent thrombosis from forming in narrowed vessels. On the basis of the understanding of abnormalities of the vascular endothelium, three classes of pulmonary vascular vasodilating drugs have been studied for the treatment of PH: prostacyclin analogs, endothelin receptor antagonists

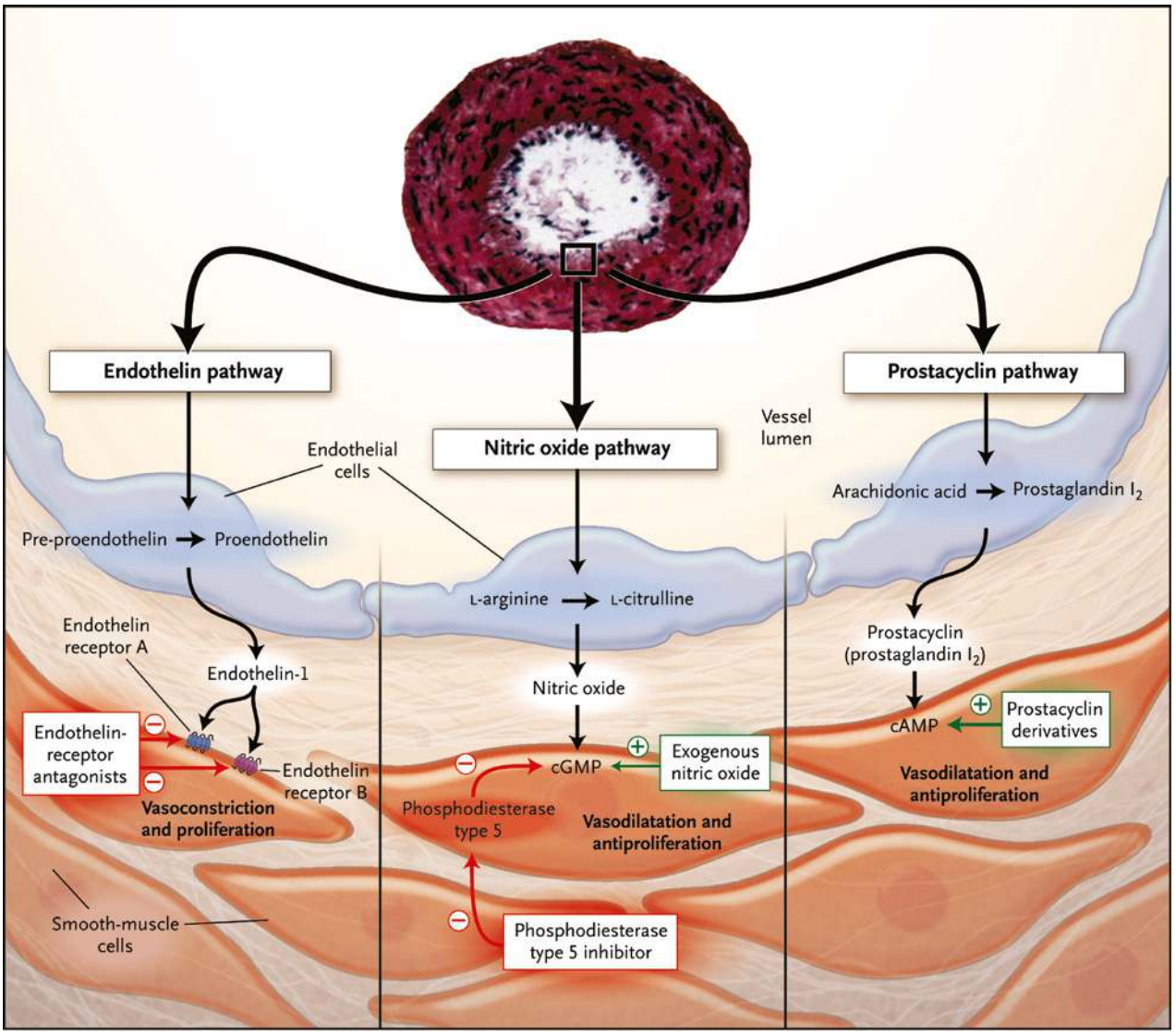


Figure 33.6 Therapeutic drug targets in pulmonary arterial hypertension. At the top of the figure, a transverse section of a small pulmonary artery from a patient with severe PAH shows intimal proliferation and medial hypertrophy. Dysfunctional pulmonary-artery endothelial cells (blue) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1 – a condition promoting vasoconstriction and proliferation of smooth muscle cells in the pulmonary arteries (red). (Source: Humbert et al. [67]. Reproduced with permission of Massachusetts Medical Society.)

(ERAs), and phosphodiesterase-5 inhibitors (PDE-5i; Figure 33.6) [67–69]. The beneficial effects of these drugs, including increased exercise capacity, improved quality of life, and increased survival, have been demonstrated mainly in adults. Due to the complex etiology and relative lack of data in children with PH, the selection of appropriate therapies remains difficult. A treatment algorithm based on expert opinion was proposed at the WSPH in 2018 (Figure 33.7) [9].

The ultimate management goals of PH in children are to increase survival and allow the normal activities of childhood without the need to self-limit. Supportive therapies may include the use of oxygen, anticoagulants, and digoxin. Diuretics may be used, but care should be taken not to decrease intravascular volume due to the preload dependence of the right ventricle. Although no controlled data exist, vaccination against influenza and pneumococcal disease is recommended in children and adults with PH, and respiratory syncytial virus (RSV) prophylaxis should be considered in infants with PH [70, 71].

Calcium channel blockers (CCBs)

Acute responders to vasodilator testing are treated with CCB such as amlodipine, nifedipine, and diltiazem. CCB inhibits the calcium influx through the slow channel into the cardiac and smooth muscle cells, causing relaxation of the pulmonary vascular smooth muscle. Adults with IPAH, who were acute responders to vasodilator testing and treated with CCB, showed improved 5-year survival (94%) compared to those not treated with CCB (55%) [72]. However, because CCB may have negative inotropic effects in young children, they should be avoided until the child is older than 1 year [62, 73].

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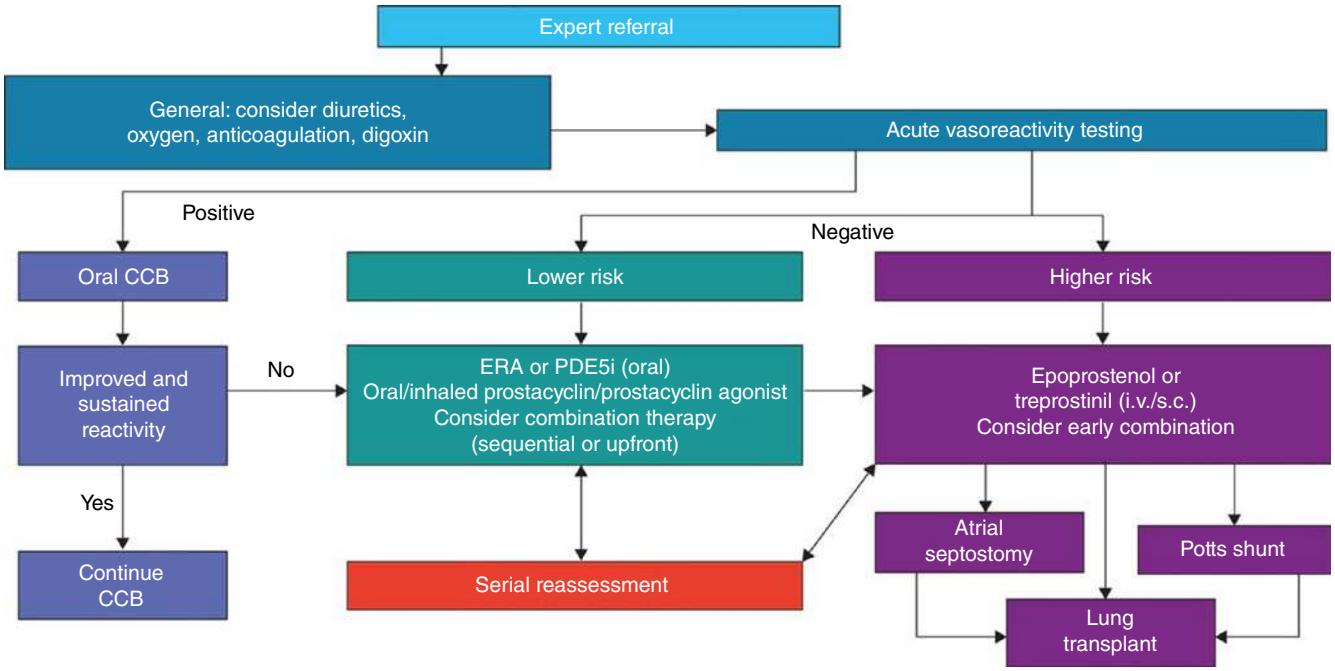


Figure 33.7 World Symposium on Pulmonary Hypertension 2018. Pediatric idiopathic/familial pulmonary arterial hypertension treatment algorithm. CCB, calcium channel blocker; ERA, endothelin receptor antagonist; IV, intravenous; PDE5i, phosphodiesterase type 5 inhibitor; SC, subcutaneous. (Source: Rosenzweig et al. [3]. Reproduced with permission of European Respiratory Society.)

Prostanoids

Patients with PH have reduced expression of prostacyclin synthetase in pulmonary arteries [74]. The prostanoids, which are prostacyclin analogs, act via cyclic AMP in the smooth muscle cell to produce vasodilation. They may also have some antiproliferative effects.

Epoprostenol (Flolan®)

This prostacyclin analog has a very short half-life (3–6 minutes) and needs to be administered continuously, usually through a permanent central venous catheter. Side effects include facial flushing, headache, jaw pain, and abdominal pain.

Treprostinil (Remodulin®, Tyvaso®)

This prostacyclin analog has a longer half-life (4–5 hours) but needs to be administered by subcutaneous injection. Pain at the injection site severely limits the use of this drug in children. For those able to tolerate frequent subcutaneous injections, the side effects are similar to epoprostenol. Other administration routes are under investigation, and the inhaled route has been shown to be effective [75–77].

Iloprost (Ventavis®)

This prostacyclin analogue is delivered by the inhaled route, and because of its short half-life (20–30 minutes), it needs to be administered six to nine times/day. This frequency of administration, in addition to the side effect of increased lower airway reactivity, has limited its use in the chronic treatment of children with PH [78].

Endothelin receptor antagonists (ERA)

Endothelin is a potent endogenous vasoconstrictor that acts via the endothelin type 1 receptor (ET). This ET receptor has two subtypes, ET_A and ET_B, which are present in pulmonary vascular smooth muscle cells, producing vasoconstriction when activated. ET_B receptors are also present in the pulmonary vascular endothelium and when activated produce vasodilation. Despite the differences in receptor subtype activity depending on location, both nonselective ET_A/ET_B receptor antagonists [*Bosentan* (Tracleer®)] and selective ET_A receptor antagonists [*Ambrisentan* (Letairis®)] are similarly effective in patients with PH. Both ERA may be administered via the oral route and require close monitoring of liver function tests.

Phosphodiesterase-5 inhibitors (PDE-5i)

Nitric oxide acts via a cyclic GMP (cGMP) pathway in the pulmonary artery smooth muscle cell to produce vasodilation. This pathway may be stimulated directly with iNO or the breakdown of cGMP may be inhibited by PDE-5i, resulting in increased cGMP and pulmonary vascular vasodilation. These inhibitors also have antiproliferative effects.

Sildenafil (Revatio®)

Sildenafil is an oral PDE-5i usually administered three times daily. Pediatric PH treatment with sildenafil has changed significantly since the STARTS 1 and 2 trials (Sildenafil in Treatment Naïve Children with PH) [79]. These trials were worldwide, randomized, double-blind, placebo-controlled studies of oral sildenafil monotherapy in low, medium, and

high doses. The studies found that functional capacity only improved with high dose sildenafil and PVR improved with medium and high dose sildenafil, but mPAP was lower only with medium dose sildenafil. However, hazard ratios for mortality were 3.95 for high versus low dose and 1.92 for medium versus low dose. Review of these data by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) resulted in different recommendations. Sildenafil was approved for use by the EMA in 2011 with a warning on avoiding higher doses. In 2012, the FDA issued a warning against the use of all doses of sildenafil for children with PH [80, 81].

Tadalafil (Adcirca®)

Tadalafil is an oral PDE-5i that has the advantage of once daily administration. Its side effect profile is similar to sildenafil including headache, flushing, nausea, myalgia, and nasal congestion [82].

Atrial septostomy and lung transplantation

Atrial septostomy performed in the cardiac catheterization laboratory should be considered in the child with worsening PH despite optimal medical therapy. The resulting improvement in cardiac output with decompression of the right heart is at the expense of hypoxemia. Features of a high-risk patient for this procedure include high right atrial pressure and low cardiac output, both of which increase mortality 5–15% [83]. Atrial septostomy may be considered as an initial procedure or as a bridge to lung transplantation. An alternative procedure that has been described as an option for patients with severe PH is the creation of a reverse Potts Shunt. This shunt is a window created between the left pulmonary artery and the descending aorta, which equalizes the pulmonary and systemic arterial pressures (Figure 33.8) [84, 85]. The use of a reversed Potts shunt in suprasystemic PH is considered advantageous compared with atrial septostomy, as it provides high oxygen saturated blood to the coronary arteries and brain, but delivers desaturated blood to the lower body. Another benefit is hemodynamically there is relief of RV pressure overload in systole, and in part, also in diastole, with a subsequent reduction in interventricular septal shift toward the left ventricle with an improvement in LV performance. However, under conditions when the PAP falls below systemic pressure, there is a risk of reversing blood flow through the shunt, creating a left-to-right shunt which could be deleterious to the pulmonary circulation by volume loading the pulmonary arterial bed. Consequently, intermittent assessment of flow direction and patterns through the Potts anastomosis with advanced 4D-Flow MRI may help guide treatment decisions [54] (Figure 33.5). The Potts shunt may be created surgically via a sternotomy or thoracotomy or percutaneously in the cardiac catheterization laboratory. This is a very high-risk procedure with a mortality of 15% [86]. The anesthetic techniques used have been recently described and include a balanced and slowly titrated anesthetic with high-dose opioids and anesthetic agents such as etomidate and ketamine to support blood pressure. Transesophageal echocardiography is helpful to monitor cardiac function and assess the aortic flow pattern. It also helps the placement of the arterial cannula if VA-ECMO is needed emergently. Near infrared spectroscopy (NIRS) is valuable, as the difference between cerebral and renal NIRS values can indicate the adequacy of the Potts's shunt [87, 88]. The optimal timing of these procedures is unclear. End-stage options for worsening PH unresponsive to therapy are lung or heart–lung transplantation. The median survival after lung transplantation in children is 4.9 years [89]. See Chapter 32 for additional discussion of lung transplantation.

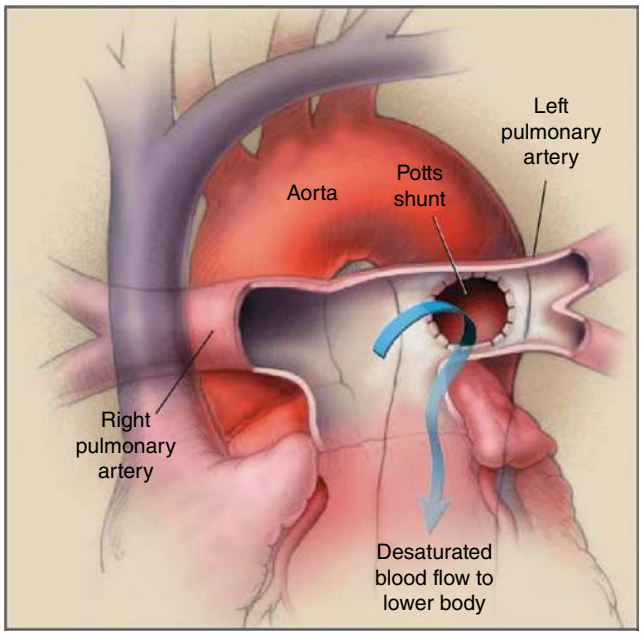


Figure 33.8 The Potts shunt procedure. The left pulmonary artery is anastomosed to the descending aorta, allowing the desaturated blood to go from the left pulmonary artery to the lower part of the body (arrow). In this drawing, the right pulmonary artery passes in front of the ascending aorta because an arterial-switch procedure had been performed in this early case report of two children who had suprasystemic pulmonary hypertension and right ventricular failure several years after an arterial switch surgery for transposition of the great arteries. (Source: Blanc et al. [84]. Reproduced with permission of Massachusetts Medical Society.)

KEY POINTS: MEDICAL MANAGEMENT OF PH

- Three classes of pulmonary vascular vasodilating drugs are available for the treatment of PH: prostacyclin analogs, ERAs, and PDE-5 inhibitors.
- CCBs are selectively used for outpatient PH treatment in patients who have a positive response during acute vasoreactivity testing.
- Inhaled nitric oxide is an effective selective pulmonary vascular vasodilator and is frequently used in the perioperative management of patients with PH.
- End-stage management strategies include atrial septostomy, a reverse Potts shunt and lung transplant.

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Perioperative risk considerations

Children with PH are at risk of experiencing major perioperative cardiovascular adverse events, including cardiac arrest and death. Data from the Pediatric Perioperative Cardiac Arrest (POCA) registry suggest that a benchmark estimate of the incidence of perioperative cardiac arrest in all pediatric patients is 0.014% [90]. In comparison, children with PH experienced an incidence of perioperative cardiac arrest of 1.6% associated with all types of procedures and 10% associated with major surgical procedures, including cardiac surgery [91]. In a report of anesthesia-related mortality in children, PH was found to be present in half of the deaths [92]. Preoperative PH has been shown to be a significant contributor to perioperative death associated with pediatric open cardiac surgery [93].

The presence of PH also adds significantly to perioperative risk in children undergoing cardiac catheterization (Table 33.8). The incidence of cardiac arrest among all children undergoing cardiac catheterization was reported to be 0.45% [94] and 0.96% [95]. This incidence increased significantly when only children with PH undergoing cardiac catheterization were considered, with reports of 0.8% [91], 1.2% [66], 2.9% [97], and 5.7% [98].

Major complications are directly associated with the severity of PH, with suprasystemic PH patients experiencing a disproportionally greater incidence than those with systemic or subsystemic PH (Figure 33.9) [66, 96, 97, 99]. Factors contributing to perioperative risk in children with PH can be categorized into hemodynamic factors, patient factors, procedural factors, and anesthetic factors [100]. These are multiple, interactive, and additive (Table 33.9).

Table 33.8 Estimated incidence of perioperative cardiac arrest and death in children with pulmonary hypertension (PH) compared with all children

Population (reference)	Procedures (*n*)	Cardiac arrest (%)	Death (%)
All children [90]	All types (1,089,200)	0.014	0.004
Children with heart disease [94]	Cardiac catheterization (4,454)	0.49	0.08
Children with heart disease [95]	Cardiac catheterization (7,289)	0.96	0.05
Children with PH [66]	All except cardiac surgery (256)	1.17	0.78
Children with PH [96]	All except cardiac surgery (148)	4.7	1.4
Children with PH [91]	All types (192)	1.6	0
Children with PH [97]	All except cardiac bypass (284)	2.11	1.06
Children with PH [66]	Cardiac catheterization (141)	2.13	1.42
Children with PH [98]	Cardiac catheterization (70)	5.71	1.43
Children with PH [97]	Cardiac catheterization (168)	2.98	1.19
Children with PH [91]	Major surgery (20)	10	0

Pulmonary hypertensive crisis

Cardiac arrest in children with PH is often immediately preceded by an acute pulmonary hypertensive crisis, in which an acute increase in PVR leads to RV failure and a decrease in cardiac output. The right ventricle dilates and encroaches on the left ventricle, thus decreasing LV stroke volume, cardiac output, and mean systemic arterial pressure (MAP). Systemic hypotension then causes a decrease in coronary perfusion pressure, which exacerbates RV failure and causes biventricular ischemia. Monitors will demonstrate an increase in PAP accompanied by decreases in SpO_2 and systemic blood pressure due to inadequate pulmonary blood flow and left heart filling. The self-perpetuating cycle of biventricular failure associated with a pulmonary hypertensive crisis is illustrated in Figure 33.10.

A pulmonary hypertensive crisis can be triggered by several stimuli that directly affect PVR or ventricular function (Box 33.5). The best known stimuli of increased PVR are hypoxia and acidosis, as demonstrated by the classic work of Rudolph (Figure 33.11) [101]. Subsequent confirmatory investigations have shown that low alveolar oxygen tension (P_AO_2) and respiratory acidosis due to hypercarbia are significant stimuli for pulmonary vasoconstriction (Figure 33.12) [102, 103]. Noxious tracheal stimulation is another known factor, as tracheal suctioning in the postoperative intensive care unit triggered a 70% increase in PVR and PAP in children with a history of PH [104]. Systemic hypotension caused by a decrease in SVR, stroke volume, or myocardial contractility can lead to inadequate coronary perfusion and RV ischemia and failure, thus triggering a pulmonary hypertensive crisis at another point in the cycle.

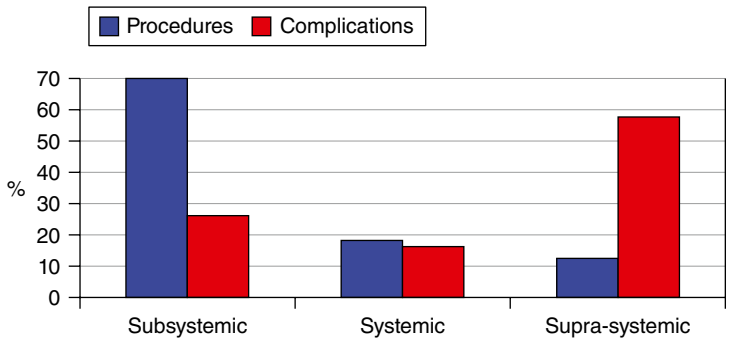


Figure 33.9 The incidence of complications increases with the severity of pulmonary hypertension. (Source: Carmosino et al. [66]. Reproduced with permission of Wolters Kluwer Health, Inc.)

Table 33.9 Perioperative risk factors for patients with pulmonary hypertension

Hemodynamic factors	Patient factors	Procedural factors	Postsurgical risks	Anesthetic factors
CI <2.5 L/min/m^2	Recent onset or exacerbation of PH	Major surgery	Hypovolemia	General anesthesia
PAP/SAP ratio >0.75	Age <1 year	Interventional cardiac cath	Systemic inflammation	ASA physical status >III
RAP >10–15 mmHg	Syncope	Long duration of procedure	Excessive pain	Unstable
PVRi >15 WU m^2	RV failure	Emergency procedure	Airway compromise	Difficult airway
Severe RV dysfunction	Failure to thrive			High opioid requirement
TAPSE <10 mm	WHO functional class III or IV			
S/D ratio >1.4 (TR jet)	BNP >59.5 pg/mL			
Pericardial effusion	Significant comorbidities			
	Chronic lung disease			
	Intercurrent illness			
	Abrupt withdrawal of PH therapy			
	Treatment-naïve patients			

Source: Adapted from Latham and Yung [100].
BNP, brain natriuretic peptide; CI, cardiac index; PAP, pulmonary artery pressure; PH, pulmonary hypertension PVRi, indexed pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; S/D, systolic/diastolic ratio; SAP, systemic arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitant; WHO, World Health Organization.

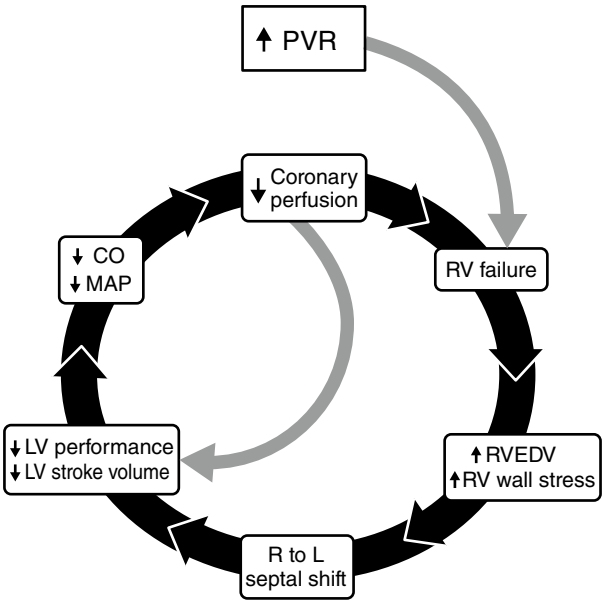


Figure 33.10 The self-perpetuating cycle of a pulmonary hypertensive crisis. The cycle can be entered at any point and culminates with cardiac arrest. (Source: Figure supplied by Dr. Mark Twite and Dr. Robert Friesen.)

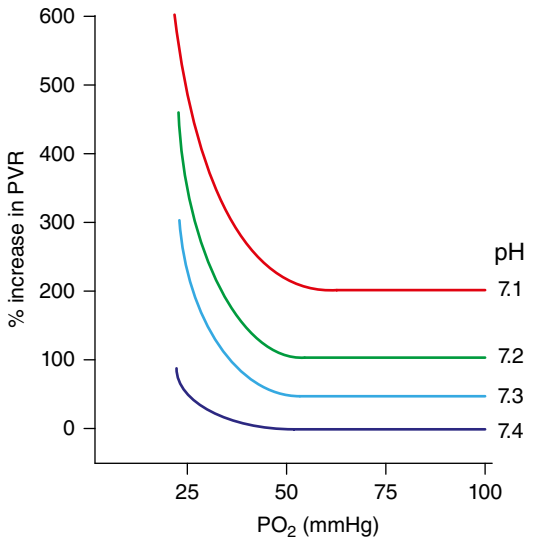


Figure 33.11 Pulmonary vascular resistance (PVR) increases with hypoxia and acidosis. (Source: Rudolph and Yuan [101]. Reproduced with permission of American Society for Clinical Investigation.)

Box 33.5: Triggering stimuli for perioperative pulmonary hypertensive crisis

- Hypoxia
- Acidosis
- Hypercarbia
- Noxious stimuli: pain, tracheal suctioning, agitation
- Hypotension

Treatment of a pulmonary hypertensive crisis is directed toward ameliorating the stimulating event and stabilizing hemodynamics (Table 33.10). Moderate hyperventilation with 100% oxygen, treatment of both respiratory and metabolic acidosis, and removal or attenuation of precipitating stimuli should be undertaken. An inhaled pulmonary vasodilator should be administered. Acute intravenous administration of pulmonary vasodilators can be associated with systemic hypotension, which may worsen coronary perfusion, so CCBs, sildenafil, and magnesium are generally not indicated for emergency treatment. Furthermore, pulmonary

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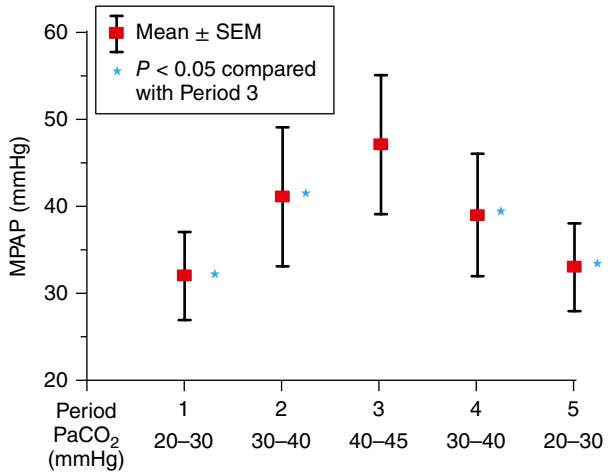


Figure 33.12 Pulmonary artery pressure (MPAP) is directly related to $PaCO_2$. (Source: Morray et al. [103]. Reproduced with permission of Elsevier.)

Table 33.10 Treatment of a pulmonary hypertensive crisis

Treatment	Rationale
Administer 100% O_2	↑ P_AO_2 and P_aO_2 can ↓ PVR
Hyperventilate	PVR is directly related to P_aCO_2
Exclude pneumothorax	Optimize ventilation
↓ Mean airway pressure	Avoid $P_{alv} > P_{art}$
Correct metabolic acidosis	PVR is directly related to H^+ level
Administer pulmonary vasodilators	iNO
Support cardiac output	Adequate preload and inotropic support, ECMO
Support coronary perfusion	Maintain SVR with epinephrine or vasopressin
Analgesia	Decrease sensory/sympathetic mediated ↑ PVR

P_AO_2, alveolar oxygen pressure; P_aO_2, arterial oxygen pressure; PVR, pulmonary vascular resistance; P_aCO_2, arterial carbon dioxide pressure; P_{alv}, alveolar pressure; P_{art}, arterial pressure; H^+, hydrogen ion; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation; SVR, systemic vascular resistance.

hypertensive crises have been observed to follow initiation of treatment of PH with intravenous prostacyclin analogs. Therefore, it is preferable in an urgent setting to administer pulmonary vasodilators by inhalation. This reduces the risk of systemic hypotension and coronary hypoperfusion by delivering the drug to the target pulmonary vasculature. In addition, the delivery of inhaled pulmonary vasodilators to well-ventilated regions of the lung may benefit oxygenation by improving ventilation/perfusion matching. The standard for inhaled pulmonary vasodilators is iNO, but inhaled prostacyclin analogs, especially iloprost, are also effective in this and similar settings [76, 105, 106].

Early treatment of bradycardia with atropine or another chronotropic drug can be helpful. If systemic hypotension persists following administration of pulmonary vasodilators, inotropic support is indicated. Epinephrine infusion is a good choice for inotropic support during emergent treatment of a pulmonary hypertensive crisis because it will improve ventricular function and raise MAP while reducing the PVR/SVR ratio [107, 108]. Other inotropic drugs have potential disadvantages in this clinical situation. Dopamine can increase the PVR/SVR ratio [107, 109]. Dobutamine can decrease SVR (and coronary perfusion), as can loading doses of milrinone and levosimendan, often requiring coadministration of a vasopressor.

In addition to inotropic support, a systemic vasopressor can improve coronary perfusion and ventricular function by supporting SVR and may avert cardiac arrest. For this purpose, arginine vasopressin and its synthetic analog, terlipressin, which increase SVR but not PVR [110–112], are preferable to phenylephrine, which is both a pulmonary and systemic vasoconstrictor [110, 113]. Although norepinephrine is used less frequently in children, its pressor effects are favorable, as MAP is increased while the PVR/SVR and PAP/SAP ratios are decreased [113–115].

Once the cycle of increased PVR and decreased ventricular function begins, however, cardiac arrest may be difficult to prevent. If cardiac arrest occurs, Pediatric Advanced Life Support guidelines for cardiopulmonary resuscitation should be followed [116]. Cardiac arrest associated with a pulmonary hypertensive crisis can be difficult to treat, and emergent use of ECMO may be necessary [117]. If emergent ECMO is required, improved outcomes are associated with shorter duration of cardiopulmonary resuscitation prior to ECMO [118], so an institutional protocol that anticipates the need for emergent ECMO in these situations is desirable.

KEY POINTS: PERIOPERATIVE RISK

- Children with PH are at increased risk of cardiac arrest and death under anesthesia. Those with suprasystemic PH are at greatest risk.
- Acute pulmonary hypertensive crisis is life-threatening, creating a cycle of ventricular failure, hypoxia, and cardiac ischemia. Triggering stimuli should be avoided, and treatment immediately started.
- Institutions caring for patients with severe PH should have experience in the emergent use of ECMO in these patients.

Anesthetic management

Anesthetic management of the child with PH requires thoughtful preparation regarding the choice of anesthetic drugs, airway management, avoidance of triggering stimuli, prophylactic pulmonary vasodilators, and appropriate monitoring (Box 33.6).

Hemodynamic effects of anesthetic drugs

The ideal anesthetic drug for children with PH would have pulmonary vasodilating effects, would not depress cardiac contractility, would maintain SVR and cardiac output, and would be short lasting and easy to titrate. Such an anesthetic

Box 33.6: Anesthetic management of the child with pulmonary hypertension

- Perioperative inhaled selective pulmonary vasodilator
- Avoid triggers of pulmonary hypertensive crisis
- Balanced anesthetic technique
- Airway and ventilatory support as appropriate for procedure
- Appropriate monitoring

Table 33.11 Expected hemodynamic effects of anesthetic drugs

	Contractility	MAP	SVR	PAP	PVR	HR
Halothane	↓↓	↓↓	↓↓	↓	↓	↓↓
Isoflurane	→	↓	↓↓	↓	↓	↑
Sevoflurane	↓	↓	↓	↓	↓	↑
Desflurane	→	↓	↓	↓	↓	↑
Propofol	↓	↓↓	↓↓	↓	↓	↓
Ketamine	→[a]	→	→	→	→	↑
Etomidate	→	→	→	↑	↑	→
Dexmedetomidine	→	↑[b]	↑	→	→	↓↓
Opioids	→	→	→	→	→	↓
Benzodiazepines	→	→	→	→	→	→

HR, heart rate, MAP, mean arterial pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; ↓, decrease; ↑, increase; →, no significant change.

[a] Ketamine can depress contractility in vitro and in catecholamine depleted patients.

[b] Dexmedetomidine can increase MAP during loading dose administration.

agent, unfortunately, does not exist. Most anesthetics are associated with undesirable hemodynamic effects – depending on dose and speed of administration – by altering heart rate or rhythm, cardiac contractility, SVR, or PVR. Significant hypotension can be observed during the induction period when peak plasma concentrations of anesthetic drugs are present, often requiring vasopressor treatment in patients with severe PH [119]. The cardiovascular effects of anesthetic drugs are discussed in detail in another chapter, but the effects pertinent to a discussion of PH are summarized in Table 33.11 and as follows:

Volatile anesthetics cause a dose-dependent depression of cardiac contractility and a decrease of SVR [120, 121]. These generally undesired effects are usually manageable during anesthesia for children with PH when it is appreciated that they vary among the volatile anesthetics and are dose dependent. Halothane causes greater depression of contractility than the newer anesthetics, while isoflurane and halothane cause a greater decrease of SVR. Furthermore, there is evidence that the volatile anesthetics are associated with a decrease in PVR. They attenuate hypoxic pulmonary vasoconstriction during one-lung ventilation [122], and $Q_p : Q_s$ remains unchanged in children with cardiac septal defects in response to halothane, sevoflurane, and isoflurane [123]. Thus, judicious use of volatile anesthetics is an important part of a balanced anesthetic in children with PH.

Propofol causes dose-dependent depression of cardiac contractility [124]. In both adults and children with cardiac disease, propofol is associated with a marked decrease in SVR and MAP and a slight decrease in PVR and PAP [125, 126]. In adults with artificial hearts, propofol causes vasodilation of systemic resistance and capacitance vessels and a decrease in PAP) [127]. The hypotension associated with propofol can lead to decreased coronary perfusion of the hypertrophic right ventricle, so propofol should be used with caution in children with PH.

While *ketamine* is quite supportive of hemodynamic stability and is frequently recommended as an anesthetic of choice in patients with cardiovascular impairment or instability, its use in patients with PH has been debated because of conflicting results of studies conducted under a variety of conditions [128]. A marked increase in PAP and PVR has been observed during ketamine anesthesia in children with PH breathing room air through the natural airway [129–131]. On the other hand, no change in PAP or PVR has been observed in response to ketamine in children with PH during controlled ventilation or while receiving a pulmonary vasodilator, such as oxygen or sevoflurane [132, 133]. Under controlled airway and ventilation conditions in room air without coadministration of pulmonary vasodilating anesthetics, ketamine was not associated with significant changes in pulmonary hemodynamics in children with PH [134]. A meta-analysis of several studies concluded that ketamine has minimal hemodynamic effects in children with CHD and/or PH [135]. Judicious use of ketamine, therefore, has a place in a balanced anesthetic for children with PH.

Etomidate is known to support systemic hemodynamics in children undergoing cardiac catheterization [136, 137], but studies of its effect on pulmonary hemodynamics are rare. A study of adults with cardiac disease demonstrated minimal effects on PAP [138], while a pediatric study demonstrated a 28% increase in PVR [137].

Dexmedetomidine is associated with acutely decreased HR and increased MAP and SVR, followed over time by a slightly lower but generally stable MAP [139–141]. These changes appear to be dose-dependent. Despite the early significant increase in SVR, a pulmonary vasoconstrictor response was not observed in children with PH who were chronically treated with pulmonary vasodilators [141]. Information regarding dexmedetomidine use in children with severe, untreated, or unstable PH is lacking.

Opioids can be associated with a decrease in HR but otherwise have minimal hemodynamic effects. PVR remains unchanged in response to fentanyl, and pulmonary vascular responses to remifentanil are clinically insignificant in adults with artificial hearts [142, 143]. Furthermore, the increase of PVR in response to noxious stimulation can be prevented by moderately large doses of fentanyl [104]. The opioids, particularly fentanyl and remifentanil, are an important part of the anesthetic management of children with PH.

Midazolam is associated with minimal hemodynamic effects and exerts clinically insignificant effects on the pulmonary vasculature of adults with cardiac disease [144]. Midazolam's sedative and amnestic effects make it an important component of a balanced anesthetic in children with PH.

In order to minimize the undesired hemodynamic effects of a full anesthetic dose of a single anesthetic drug, it is preferable to utilize a balanced anesthetic technique. Balanced administration of subanesthetic doses of several anesthetics can achieve an adequate depth of anesthesia without the

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marked hemodynamic changes that can be associated with a high dose of a single drug. The authors generally employ midazolam, fentanyl or remifentanil, and sevoflurane or isoflurane for most procedures. High doses of fentanyl can be used for major operations if postoperative tracheal extubation is not anticipated. Judicious use of propofol at low-infusion rates can be considered, but its administration should be undertaken with caution because its depression of SVR is not short-lived. Low to moderate doses of ketamine and dexmedetomidine have been used successfully.

Sometimes, systemic hypotension can be observed despite a balanced technique, especially in children who are hypovolemic. In children with hypertrophic right ventricles, hypotension can lead to decreased coronary perfusion and acute RV failure. Judicious use of a vasoconstrictor such as epinephrine or vasopressin, therefore, can be useful when hypotension is encountered intraoperatively.

Perioperative pulmonary vasodilators

In addition to the administration of a balanced anesthetic technique and the avoidance of triggering stimuli, the risk of intraoperative pulmonary hypertensive crisis or cardiac arrest can be reduced by perioperative treatment with pulmonary vasodilator therapy. The odds ratio for children with PH to develop a major perioperative complication was only 0.31 in those who were chronically treated with a pulmonary vasodilator preoperatively [91]. When providing anesthetic care for noncardiac surgery to children with severe PH (systemic or suprasystemic) or those not treated with chronic pulmonary vasodilator therapy, the authors administer iNO perioperatively from induction of anesthesia through recovery. The iNO is delivered at a dose of 20–40 ppm through the inspiratory limb of the breathing circuit; postoperatively, it can be administered via face mask or nasal cannulae [145] and weaned in the postanesthesia care unit. Alternative methods of generating and delivering iNO are under development to improve cost and ease of administration [146, 147].

Inhaled selective pulmonary vasodilators are preferred for perioperative prophylaxis because they deliver drug selectively to the pulmonary vascular bed, thus avoiding the systemic hypotension that can occur with acute intravenous or oral administration of nonselective pulmonary vasodilators. Trials of oral sildenafil for perioperative prophylaxis in patients with PH have had mixed results [148–150]. On the other hand, intraoperative administration of inhaled aerosolized pulmonary vasodilators improved right heart hemodynamics in PH patients better than did intravenously administered pulmonary vasodilators [151]. In addition to iNO, other pulmonary vasodilators that have been shown to be effective when administered selectively by inhalation include the prostacyclin analogs epoprostenol [152], iloprost [153, 154], and treprostinil [77], the phosphodiesterase inhibitor milrinone [155], and the nitric oxide donor nitroglycerin [155]. Of these, iloprost has emerged as a reasonable alternative to iNO for prophylactic perioperative inhaled drug therapy for children with PH [105, 106].

One caveat regarding pulmonary vasodilator therapy is that in patients whose PH is caused by congenital postcapillary obstructive lesions (Group 2.4 of the 2018 Pulmonary Hypertension Classification), as shown in Table 33.2. Pulmonary vein stenosis, which has a very poor prognosis, is emerging as an important cause of sustained PH, especially in the setting of ex-premature infants with BPD) [156]. Administration of a pulmonary vasodilator can dilate the pulmonary arteries without relieving the obstruction to flow, thereby causing acute pulmonary edema and clinical deterioration. However, there is some limited evidence that iNO has improved pulmonary hemodynamics in select patients following interventional balloon dilation of pulmonary vein stenosis [157]. Another caveat regarding iNO use is that rebound PH following weaning of iNO can occasionally occur, especially after prolonged administration or a severe pulmonary hypertensive episode, and may require treatment with another vasodilator to facilitate weaning [158, 159].

Airway and ventilation management

Airway management techniques by the anesthesiologist are chosen as appropriate for the surgical procedure. Although case reports have described pulmonary hypertensive crises in association with tracheal intubation [160, 161], the reports suggest that the patients were either inadequately anesthetized or that the intubation occurred after hemodynamic deterioration had begun. When used alone, intravenous fentanyl 25 mcg/kg attenuates the significant increase in PAP and PVR in response to tracheal suctioning or intubation in children with PH [104, 160]. In the authors' experience, a balanced general anesthetic employing remifentanil or a lower dose of fentanyl as a component will achieve the same goal. The incidence of complications in children with PH undergoing noncardiac surgery or cardiac catheterization was found to be independent of the method of airway management (natural airway, laryngeal mask airway, or endotracheal tube) [66, 97]. Tracheal intubation was preferred in a study of children with PH undergoing noncardiac procedures [96]. Therefore, with adequate topical and general anesthesia, the authors do not hesitate to intubate the trachea when indicated for the surgical procedure or condition of the patient and believe that intubation provides the important benefit of control of the airway and ventilation.

Alternatively, airway management with a face mask, laryngeal mask airway, or the natural airway (with end-tidal CO_2 monitoring via nasal cannula) can be employed when indicated and appropriate for the procedure. It should be remembered that hypoxia and hypercarbia can trigger a pulmonary hypertensive crisis and that airway obstruction or hypoventilation can occur during some sedative and anesthetic management techniques [162]. Thus, the anesthesiologist should consider all options for airway access and ventilatory management.

Ventilatory support should be provided as needed with the goals of maintaining appropriate lung volumes and blood gases. PVR is increased at both very small and very large lung volumes and is lowest at functional residual capacity (Figure 33.13) [163]. Prevention of atelectasis by keeping lung volumes above closing capacity and avoidance of excessive tidal volume are, therefore, both important. Since PVR increases during alveolar hypoxia, hypoxemia, and acidosis, normal blood gases should be maintained with appropriate ventilatory and airway management. Factors that increase RV afterload, such as high PEEP, one-lung

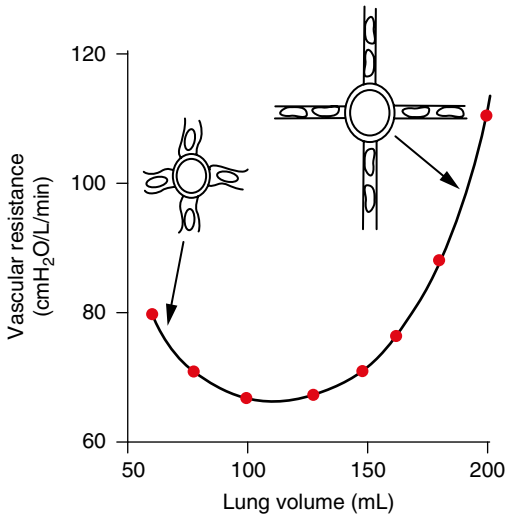


Figure 33.13 Pulmonary vascular resistance (PVR) increases in association with very small and very large lung volumes. At low volumes, PVR is high because the extra-alveolar vessels become narrow. At high volumes, the capillaries are stretched, and their caliber is reduced. (Source: West [163]. Reproduced with permission of Wolters Kluwer Health, Inc.)

ventilation, patient position, and surgical manipulation, should be anticipated and minimized [164].

Monitoring

The American Society of Anesthesiologist guidelines for intraoperative monitoring should be followed. Invasive monitors are used as appropriate for the patient's status and planned procedure. Despite the known risks of pulmonary artery catheters, they provide valuable hemodynamic information, and limited evidence supports their use during major surgical procedures and intensive care of children with PH [165, 166].

Echocardiography offers noninvasive assessment of patients with PH, and both transthoracic and transesophageal echocardiography have been utilized as intraoperative monitors. Estimation of RV systolic pressure can be made by applying Bernoulli's equation to measurement of the tricuspid valve regurgitant jet velocity (Figure 33.3; Box 33.2). The extent of RV dilation and right-to-left interventricular septal shift, as well as biventricular function, can be readily assessed subjectively (Figure 33.14). This is important, as greater RV encroachment on LV volume is associated with greater risk of perioperative adverse events in children with PH [97].

Postanesthesia disposition

The high risk of major cardiovascular adverse events associated with PH continues during the postoperative period [96, 167]. Therapeutic or prophylactic drugs administered intraoperatively, such as iNO and oxygen, should be continued postoperatively and weaned gradually, as the child awakens and remains stable. The possibility of rebound PH following weaning of iNO, especially after prolonged administration or a severe pulmonary hypertensive episode,

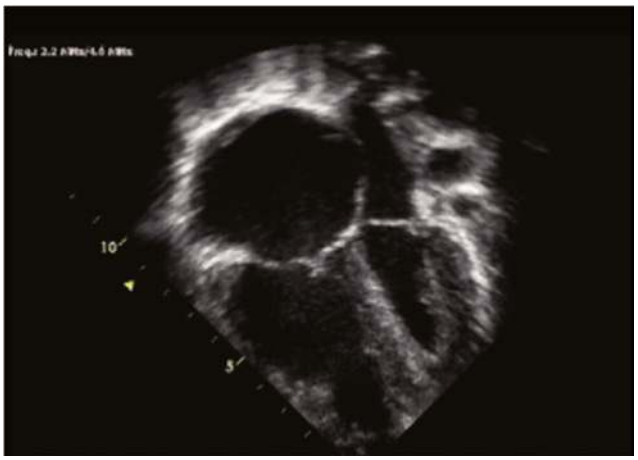


Figure 33.14 The leftward shift of the interventricular septum due to right ventricular dilation causes a reduction in left ventricular stroke volume. (Source: Figure supplied by Dr. Mark Twite and Dr. Robert Friesen.)

should be kept in mind. All precautions should be taken to avoid hypoxemia, hypotension, and hypovolemia. Control of postoperative pain and nausea should be effective. Evidence-based guidelines for postanesthetic disposition of PH patients are lacking, but a proposal based on patient, procedural, and anesthetic risk factors has been offered [168]. Higher risk patients (e.g. systemic or suprasystemic PH, impaired RV function, major surgical procedure, unstable) are admitted directly to the ICU. Lower risk patients (e.g. subsystemic PH, uneventful intraoperative course, minor procedure) can be admitted to the PACU. Following recovery from anesthesia, stable patients in the PACU who have undergone minor procedures without complications can be discharged. It is advisable to admit others to a monitored bed where rapid medical response is possible. There is subjectivity in these decisions; when in doubt, err on the side of safety.

KEY POINTS: ANESTHETIC MANAGEMENT OF PH

- Anesthetic management requires thoughtful preparation regarding the choice of anesthetic drugs, airway management, avoidance of triggering stimuli, prophylactic pulmonary vasodilators, and appropriate monitoring.
- There is no single ideal anesthetic agent for patients with PH. Instead, a balanced anesthetic technique should be adopted using several anesthetic agents to avoid adverse hemodynamic effects.
- The high risk of major cardiovascular adverse events associated with PH continues during the postoperative period. During recovery, all precautions should be taken to avoid hypoxia, hypercarbia, and hypotension, and the control of pain and nausea should be adequate. Final disposition, whether it is being discharged home or admitted to a monitored bed or the ICU should be decided based on individual patient, procedural, and anesthetic risk factors.

Conclusions

PH is a common occurrence in patients with CHD, and it also affects many other children, especially those born prematurely with underdeveloped lungs and patients with other causes of chronic hypoxia. Idiopathic and inherited forms of PH are less common. Recent advances in the understanding of pathophysiology, classification, and medical therapy have led to increased survival in this population. Many of these children should be cared for by congenital cardiac anesthesiologists who are familiar with the pathophysiology of PH and the increased risk of anesthesia in this population. Anesthetic management requires thoughtful preparation regarding the choice of anesthetic drugs, airway management, avoidance of triggering stimuli, prophylactic pulmonary vasodilators, appropriate monitoring, the use of a balanced anesthetic technique, and the ability to rescue the patient during a pulmonary hypertensive crisis. The patient should be monitored closely in an appropriate location after their procedure.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913. This article discusses the current definitions and classification of pulmonary hypertension.

4 Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:1801916. This article discusses recent advances, ongoing challenges, and distinct approaches for the care of children with pulmonary hypertension, as presented by the Pediatric Task Force of the 6th World Symposium on Pulmonary Hypertension. The article provides updates on the current definition, epidemiology, classification, diagnosis, and treatment of pediatric pulmonary hypertension and identifies knowledge gaps.

13 Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132(21):2037–99. In a joint effort from the American Heart Association and American Thoracic Society, a panel of experienced clinicians and clinician-scientists was assembled to review the current literature and to make recommendations on the diagnosis, evaluation, and treatment of pediatric pulmonary hypertension. This publication presents the results of extensive literature reviews, discussions, and formal scoring of recommendations for the care of children with pulmonary hypertension.

14 Hemnes AR, Beck GJ, Newman JH, et al. PVDOMICS: a multi-center study to improve understanding of pulmonary vascular disease through phenomics. Circ Res 2017;121 (10):1136–9.The NIH/NHLBI launched an initiative, "Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics (PVDOMICS)" that aims to augment the current PH classification based on shared biological features. This article presents the project and discusses the 'omics' analysis plan.

47 Truong U, Meinel K, Haddad F, et al. Update on noninvasive imaging of right ventricle dysfunction in pulmonary hypertension. Cardiovasc Diagn Ther. 2020;10(5):1604–24. Safe, accurate imaging modalities are critical for the diagnosis, serial monitoring and tailored therapy of patients with pulmonary hypertension. While cardiac catheterization remains the conventional modality for establishing diagnosis and monitoring, noninvasive imaging has gained considerable momentum in providing accurate assessment of the entire RV-pulmonary axis. This review discusses the most recent developments in echocardiography, MRI and CT in the evaluation of pulmonary hypertension in children and adults.

66 Carmosino MJ, Friesen RH, Doran A, Ivy DD. Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. Anesth Analg 2007;104(3):521–7. This study documents the significantly increased risk of cardiac arrest associated with anesthesia for children with pulmonary hypertension.

100 Latham GJ, Yung D. Current understanding and perioperative management of pediatric pulmonary hypertension. Paediatr Anaesth 2019;29(5):441–56. This up-to-date review summarizes the current understanding of pediatric pulmonary hypertension physiology, perioperative risk stratification, anesthetic risk, and intraoperative considerations.

101 Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes. J Clin Invest 1966;45(3):399–411. This classic paper describes the relationship between pulmonary vascular resistance and hypoxia and acidosis.

106 Kaestner M, Schranz D, Warnecke G, et al. Pulmonary hypertension in the intensive care unit. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102(Suppl 2):ii57–66. This expert consensus statement was produced by the European Paediatric Pulmonary Vascular Network and endorsed by the International Society of Heart and Lung Transplantation (ISHLT) and the German Society of Paediatric Cardiology (DGPK). The consensus statement focuses on the management of acute severe pulmonary hypertension in the intensive care unit and provides management algorithms.

111 Siehr SL, Feinstein JA, Yang W, et al. Hemodynamic effects of phenylephrine, vasopressin, and epinephrine in children with pulmonary hypertension: a pilot study. Pediatr Crit Care Med 2016;17(5):428–37. This prospective pilot study of phenylephrine, arginine vasopressin, and epinephrine in pediatric patients with pulmonary hypertension showed an increase in aortic pressure with all drugs although only vasopressin resulted in a consistent decrease in the ratio of pulmonary-to-systemic vascular resistance.

CHAPTER 34

Anesthesia for the Cardiac Catheterization Laboratory

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Introduction

Few areas in the field of congenital heart disease (CHD) have evolved as rapidly as the discipline of cardiac catheterization. Lesions that were previously managed with surgical intervention alone or considered inoperable altogether are now treated in the cardiac catheterization laboratory (CCL), with benefits ranging from increased survival to decreased morbidity and lengths of stay. Coincident with these advances, however, have been increases in patient acuity and complexity as well as procedural risk. For the anesthesia team, these changes have underscored the need for risk assessment and preprocedural planning to prevent adverse events, and further, awareness regarding procedure-specific complications and their management. These aspects of anesthetic care are a focus of this chapter and are presented both generally and within the context of individual procedures that may be encountered in the modern CCL.

Diagnostic catheterization

Cardiac catheterizations purely for diagnostic purposes have decreased over the years due to advances in noninvasive imaging. Nonetheless, diagnostic cardiac catheterization remains an important tool in the evaluation of the anatomy and physiology of many patients with CHD. Common indications are as follows [1]:

- To measure intravascular pressures and derive hemodynamic information, such as pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), shunt fractions ($Q_p : Q_s$), and cardiac output. Such information is necessary in the assessment of pulmonary hypertension (PH), pretransplant candidacy in children with end-stage heart disease, and the suitability for progression to the next stage of single-ventricle palliation (e.g., bidirectional Glenn or Fontan) (see Figure 34.1) [2]
- To evaluate the effects of drugs (e.g., inhaled nitric oxide [iNO]) and respiratory interventions (increasing FiO_2) on PVR in patients with PH
- To provide further anatomic definition when noninvasive imaging is inadequate. Examples include the evaluation of coronary artery anomalies or major aortopulmonary collaterals (MAPCAs)
- To perform hemodynamic assessment, endomyocardial biopsies, and coronary artery angiography as part of routine surveillance following heart transplantation. Endomyocardial biopsy is also used in the diagnosis of cardiomyopathy and viral myocarditis
- To distinguish between the diagnoses of constrictive pericarditis and restrictive cardiomyopathy

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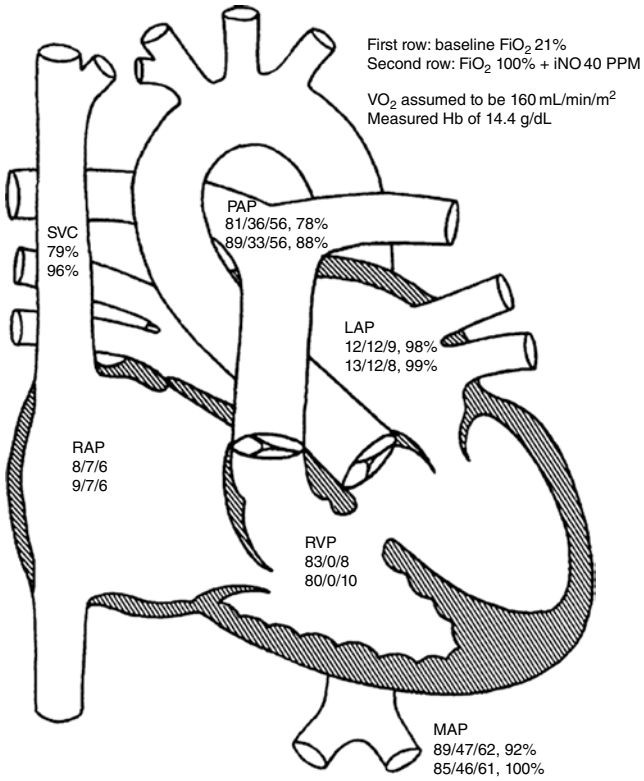


Figure 34.1 Diagnostic catheterization in a child with pulmonary hypertension. A 4-year-old child with a late diagnosis of perimembranous VSD and subsequent pulmonary hypertension presented for hemodynamic evaluation to assess candidacy for VSD closure. Measurements were taken on room air and subsequently on 100% FiO_2 and inhaled nitric oxide as part of acute vasodilatory testing (AVT). At baseline, $Q_p : Q_s$ was 0.65 : 1, indicating right-to-left shunting at the VSD, and PVRi was 11.4 Wood units/m^2. With AVT, no decrement in PAP or PVRi was noted. Surgical closure was therefore deferred and therapy for pulmonary hypertension was initiated with plans to reassess PVR in 6 months. LAP, left atrial pressure; MAP, mean arterial pressure; PAP, pulmonary artery pressure; PPM, parts per million; PVRi, pulmonary vascular resistance indexed to body surface area; RAP, right atrial pressure; RVP, right ventricle; SVC, superior vena cava; VO_2, oxygen consumption; VSD, ventricular septal defect. (Source: Mullins and Mayer [2]. Reproduced with permission of John Wiley & Sons.)

- To assist in the management and decision-making for complex CHD, either preoperatively or postoperatively (e.g., the postoperative Fontan with persistent pleural effusions without clear etiology, or the evaluation of the coronary arteries in a patient with severely depressed function following an arterial switch)
- To confirm the need for a planned intervention and assess the efficacy of the intervention once performed (e.g., closure of a cardiovascular communication)

As implied, the results of diagnostic catheterizations can have an outsized impact on the management strategy for a given patient. For example, the PVR calculation in a child presenting for a cardiac transplant evaluation may determine whether or not the child is eligible for transplantation. These stakes underscore the need to ensure that the hemodynamic variables being measured are as representative of the patient's baseline physiology as possible. For the anesthesiologist, an understanding of how airway management, common anesthetics, oxygenation, and ventilation can affect these measurements is critical (see Anesthetic techniques). A general strategy to approximate baseline physiology is to conduct the anesthetic on room air with normal ventilation while maintaining an age-appropriate blood pressure and heart rate. For patients who need oxygen (or who are on oxygen at baseline), the higher partial pressure of oxygen is accounted for in calculations of flows and resistances.

Procedure overview

The vessels most commonly accessed are the femoral vein and femoral artery. The femoral artery can be used solely for blood pressure monitoring or to evaluate the coronaries, left ventricular end-diastolic pressure (LVEDP), or MAPCAs as indicated. The internal jugular vein may be used to access the pulmonary arteries (PAs) in patients with Glenn or hemi-Fontan circulations or to facilitate procurement of endomyocardial biopsy specimens in biventricular hearts. Alternative venous approaches, such as transhepatic or transsplenic, may be indicated in children with a history of occlusions at other sites and are associated with increased risks of bleeding.

Following access, pressures and oxygen saturations are obtained in sequence throughout the cardiac, PA, and systemic arterial circulations (see Table 34.1 for normal parameters). These values are then used to calculate shunts (if present), flows (Q_p and Q_s), and resistances (PVR and SVR; see Table 34.2 for calculations). Stable hemodynamics along with constant oxygenation and ventilation (room air and normocapnea if possible) are essential during the sampling of these values.

Flows in children are most often calculated using the Fick principle, which relates oxygen consumption (VO_2) to flow. VO_2 in this equation can be measured directly using respiratory mass spectrometry or estimated using nomograms based on age, sex, and heart rate [3]. Due to ease, estimations of VO_2 are most commonly used, but by virtue of being estimations, they may introduce important error in the calculations of flow and resistance [4–9]. For example, if the estimated VO_2 is significantly higher than actual VO_2, the resulting cardiac output will be overestimated, while the calculated resistances will be underestimated.

Endomyocardial biopsy

The majority of patients undergoing endomyocardial biopsy do so uneventfully, using either general anesthesia with an artificial airway or sedation with a natural one. Certain high-risk patients, however, warrant discussion, including (i) children less than 6 months of age and less than 8 kg who due to their small size are at increased risk of complications such as ventricular perforation and significant arrhythmias [10], (ii) heart transplant patients with an active concern for rejection or a history of coronary allograft vasculopathy (CAV), and (iii) patients otherwise being evaluated for myocarditis. Children with active rejection or myocarditis may have severely depressed function with coinciding arrhythmias due to myocardial irritability. The process of placing catheters within the heart and taking biopsy specimens can further exacerbate or prompt new arrhythmias. Because of tissue friability, these patients may also be at increased risk of

Table 34.1 Normal cardiac catheterization data

	Pressure (mmHg)		
	Newborns	Older children	Oxygen saturation (%)
Right atrium			60–80
a wave	3–8	5–10	
v wave	2–6	4–8	
Mean	0–4	2–6	
Right ventricle			65–75
Systolic	65–80	15–25	
End diastolic	2–7	3–8	
Pulmonary artery			65–75
Systolic	65–80	15–25	
Diastolic	35–50	8–12	
Mean	40–70	10–16	
PA wedge			95–100
a wave	6–10	8–14	
v wave	7–11	10–17	
Mean	5–8	7–13	
Left atrium			95–100
a wave	4–7	6–12	
v wave	6–12	8–15	
Mean	3–6	5–10	
Left ventricle			95–100
Systolic	65–80	90–120	
End diastolic	3–7	2–5	
Aorta			95–100
Systolic	65–80	90–120	
Diastolic	45–60	60–75	
Mean	55–65	70–90	
Flows		L/min/m² BSA	
Pulmonary (Q_p)	3.5–5.0	3.5–5.0	
Systemic (Q_s)	3.5–5.0	3.5–5.0	
Resistances		Woods units/ m² BSA	
Pulmonary (R_p)	8–10	1–3	
Systemic (R_s)	10–15	15–30	

BSA, body surface area; PA, pulmonary artery.

myocardial perforation and tamponade. Preparation should be commensurate with the above risks and entail plans to resuscitate in the event of hemodynamic decompensation (including discussions of extracorporeal membrane oxygenation [ECMO] or prophylactic placement of percutaneous left ventricular (LV) support as a bridge to recovery). If sedation is chosen as the anesthetic technique, one should be prepared as always to escalate to general endotracheal anesthesia (GETA). Of note, in heart transplant patients with signs of heart block and/or rejection, the use of dexmedetomidine may provoke a significant bradyarrhythmia [11]. Attention to the patient's baseline electrocardiogram (EKG) and risk for heart block can inform the decision of whether or not to use this drug (see section on Anesthetic drugs). The use of dexmedetomidine in a heart transplant patient has also been associated with impaired metabolism of tacrolimus resulting in supratherapeutic levels [12]. Though not immediately relevant to anesthetic management, this risk may indicate the need for more frequent monitoring of tacrolimus levels in the postprocedural period.

CAV, or transplant coronary artery disease, is marked by the progressive obliteration of the graft's coronary vasculature and is a result of immunologic and nonimmunologic factors [1, 13]. Due to the variable reinnervation of the transplanted heart, angina may not occur to warn of its presence, and CAV may only be diagnosed incidentally during the patient's annual coronary angiography (Figure 34.2). Risk factors for CAV include rejection within the first-year post-transplant and increasing graft age [13]. Adolescents are at greatest risk, with only 50% remaining CAV free at 10 years post-transplant [14]. The patient who should raise one's concern for CAV would be a teenager several years out from transplant who on prior catheterizations had unexplained hypotension or an elevated right ventricular end-diastolic pressure (RVEDP) (potentially indicative of microvascular disease). In patients with known CAV, graft survival decreases to 50% at 5 years postdiagnosis [14]. As in any patient at risk for myocardial ischemia, anesthetic goals focus on minimizing myocardial oxygen consumption and maximizing oxygen delivery. Hypotension should be diligently avoided.

Pulmonary hypertension study

Right heart catheterization (RHC) remains the gold standard to diagnose and characterize PH, assess the response to AVT, and provide data to guide risk stratification [15] (see Table 34.3). Data is obtained at baseline (or rest) and with AVT. AVT is performed to determine the effect of pulmonary vasodilators on PVR. Protocols and the exact pulmonary vasodilators used vary, but a common process is to deliver a FiO_2 of 1.0 followed by iNO at 40 parts per million (PPM) [16]. A positive response is defined as a decrease in mean pulmonary arterial pressure (mPAP) by 10 mmHg without a fall in cardiac output [15]. The presence or absence of a response directs pharmacologic therapy and is prognostic [15, 17]. In patients with CHD with an intracardiac shunt (e.g., an older child with a large ventricular septal defect [VSD] and bidirectional shunting on echocardiography), a decrease in PVR with AVT can influence decision-making on whether or not to attempt closure (see Figure 34.1).

The utility of this data, however, needs to be weighed against procedural and anesthetic risks. Adverse events in children with PH undergoing catheterization range from 2 to 14%, with an incidence of cardiac arrest between 0.8 and 5.7% and mortality between 0 and 1.4% [18–28]. Those at greatest risk include ages <5 months and those with systemic-to-suprasystemic PAP [28, 29]. Children with newly diagnosed PH, depressed RV function (regardless of the estimated PAP on transthoracic echocardiography [TEE]), poor functional status, and need for preprocedural vasoactive and/or respiratory support represent another highly concerning group [30] (Table 34.4). In such patients, the risks of catheterization likely exceed its benefits, and empiric therapy with PH agents may be indicated to provide stability before proceeding. Decisions regarding the timing of catheterization are thus critical to minimizing risk and underscore the need for anesthesia involvement in coordinating with the pediatric PH and catheterization teams.

Coincident with decreasing risk is the maintenance of preprocedural PH therapy. Patients on oral agents are instructed

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Table 34.2 Hemodynamic calculations performed during cardiac catheterization

Flows

$$\text{Pulmonary}: Q_p = \frac{VO_2}{(S_{PV}O_2 - S_{PA}O_2) \times Hgb \times 1.34 \times 10} \text{ L/min/m}^2$$

$$\text{Systemic}: Q_s = \frac{VO_2}{(S_{AO}O_2 - S_{MV}O_2) \times Hgb \times 1.34 \times 10} \text{ L/min/m}^2$$

Resistances

$$\text{Pulmonary (PVRi)}: R_p = \frac{\text{mPAP} - \text{mPCWP (or LAP)}}{Q_p} \text{ WU/m}^2$$

$$\text{Systemic (SVRi)}: R_s = \frac{\text{MAP} - \text{mSVP}}{Q_s} \text{ WU/m}^2$$

Shunts

$$\text{Pulmonary to systemic}: \frac{Q_p}{Q_s} = \frac{S_{AO}O_2 - S_{MV}O_2}{S_{PV}O_2 - S_{PA}O_2}$$

AO, aorta; AOP, LAP, left atrial pressure; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; mSVP, mean systemic venous pressure; MV, mixed venous; PA, pulmonary artery; PV, pulmonary vein; PVRi, pulmonary vascular resistance indexed to body surface area; Q_p, pulmonary flow; Q_s systemic flow; SVRi, systemic vascular resistance indexed to body surface area; VO_2, oxygen consumption

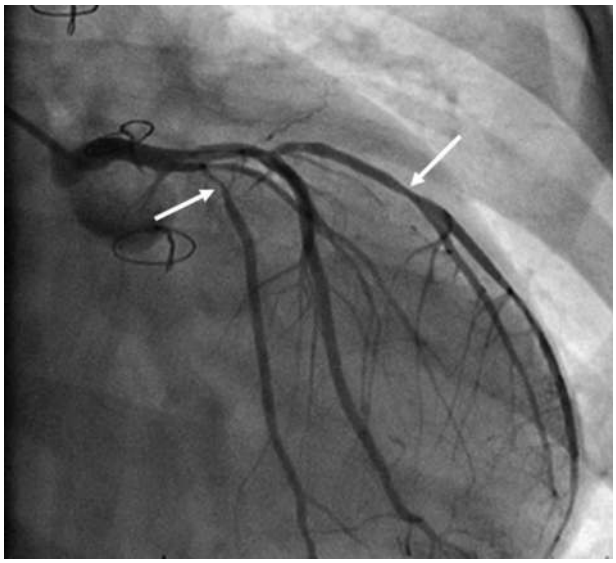


Figure 34.2 Coronary angiogram during routine post-transplant evaluation demonstrating coronary allograft vasculopathy. Arrows indicate gross areas of stenosis. The graft was 11 years old and the child was asymptomatic. He developed profound hypotension following anesthetic induction and a ventricular fibrillation arrest following angiography. He was subsequently retransplanted. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

Table 34.3 Hemodynamic definitions of pediatric pulmonary hypertension based on catheterization data

	Revised definition (at rest)	Clinical groups[a]
Precapillary PH	mPAP > 20 mm Hg PCWP ≤ 15 mm Hg PVRi ≥ 3 WU m²	1, 3, 4, and 5
Isolated postcapillary PH	mPAP > 20 mm Hg PCWP > 15 mm Hg PVRi < 3 WU m²	2 and 5
Combined precapillary and postcapillary PH	mPAP > 20 mm Hg PCWP > 15 mm Hg PVRi≥3 WU m²	2 and 5
Pulmonary hypertensive vascular disease	Biventricular circulations mPAP > 20 mm Hg PVRi≥3 WU m² Cavopulmonary circulation Mean TPG > 6 mm Hg PVRi > 3 WU m²	

Source: Modified from Rosenzweig et al. [15].
mPAP, indicates mean pulmonary arterialy pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVRi, pulmonary vascular resistance indexed to body surface area; TPG, transpulmonary gradient (mPAP – PCWP or mean left atrial pressure); WU, Wood units
[a] Group 1: PAH; Group 2: PH due to left heart disease; Group 3: PH due to lung disease and/or hypoxia; Group 4: PH due to pulmonary artery obstructions; Group 5: PH with unclear and/or multifactorial mechanisms

to take them as scheduled, including the day of the procedure. Caveats include children on iNO prior to catheterization and those on subcutaneous (SQ) infusions of treprostinil. The preprocedural use of iNO is an indicator of illness severity; however, it may be requested that iNO be turned off during the catheterization to establish baseline conditions. Doing so may induce a PH crisis, however, and is not advised in the critically ill patient. If this is nonetheless thought to be necessary, the process of decreasing iNO should be gradual and with awareness that PH crises are often prompted *not* with incremental decreases, but by going from 1 PPM to off. The team should, therefore, be prepared to reinitiate iNO and

Table 34.4 Determinants of risk in pediatric pulmonary hypertension

Lower risk	Determinants of risk	Higher risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
Normal (height/BMI)	Growth	Failure to thrive
I, II	WHO functional class	III, IV
Minimally elevated	Serum BNP/ NT-proBNP	Significantly elevated or rising
Normal RV systolic function	Echocardiography	RV systolic dysfunction
Minimal RA/RV enlargement		Severe RA/RV enlargement
RV/LV ratio <1		Increased RV/LV ratio
Normal TAPSE		Reduced TAPSE
		Pericardial effusion
CI > 3.0 L/min/m2	Invasive hemodynamics	CI < 2.5 L/min/m2
mRAP < 10 mm Hg		mRAP > 15 mm Hg
mPAP/mSAP < 0.5		mPAP/mSAP > 0.75
+ Acute vasoreactivity		PVRi > 15 WU m2

Source: Hansmann et al. [30]. Reproduced with permission of BMJ Publishing Ltd.

These determinants have only level of evidence C because of lacking pediatric data, but are informed by clinical practice and can nonetheless guide preprocedural risk assessment and preparation.

BMI, indicates body mass index; BNP, B-type natriuretic peptide; CI, cardiac index; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; PVRi, pulmonary vascular resistance indexed to body surface area; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

resuscitate as indicated. Options for the management of children on SQ treprostinil are to continue delivery as SQ or transition to intravenous (IV) administration. The rationale for the latter is a more stable and visible site for delivery (due to the risks of dislodgement of SQ sites with positioning, variability in SQ perfusion and absorption during anesthesia, and the inability to monitor if under the drapes). If maintaining the infusion SQ, there is a margin of safety even in the event of dislodgement due to treprostinil's long half-life (4 hours).

Anesthetic technique and preparation depend on patient age, comorbidities, disease severity, and institutional practice. Older adolescents or adults who are cooperative can be managed with minimal sedation and local anesthetic infiltration. Upper extremity venous access to perform RHC can be considered to minimize discomfort and the need for analgesics relative to femoral access [31]. Deeper sedation can be used safely in appropriately selected patients but requires attention to avoiding hypoxia, hypercapnea, and acidosis that may prompt either a PH crisis or skew assessment of PAP and PVR. Given the younger age of this patient population, our most common approach is to use GETA. We and others have not observed PH crises related to airway instrumentation [19, 32–34].

Anesthetic induction and maintenance are tailored to the patient's disease severity. A balanced anesthetic using a combination of opioid, ketamine, midazolam, and volatile agent is well tolerated (see Anesthetic drugs). Ketamine and dexmedetomidine do not adversely affect the pulmonary vasculature and can reduce the amount of volatile agent needed [32, 33]. Most commonly observed following induction is relative hypotension secondary to anesthesia-induced decreases in SVR, contractility, and preload (with positive pressure ventilation [PPV]). Phenylephrine boluses or infusions of vasopressin or phenylephrine are useful in increasing SVR and preventing RV ischemia that can lead to cardiovascular collapse. For high-risk patients (those with moderately to severely depressed RV function), infusions of epinephrine and/or vasopressin can be initiated prior to induction. Further, the availability of ECMO should be confirmed in advance (assuming the child is an ECMO candidate). Blood, iNO, vasoactives, adequate vascular access to deliver infusions, and defibrillation pads should be present. A dedicated arterial line should be considered. For all patients following AVT, iNO should be titrated off slowly, particularly in those who have had a positive response. Postprocedural disposition is dictated by disease severity and intraprocedural course. Our practice is conservative, and many of our PH patients are admitted to the intensive care unit (ICU) if only for observation.

Cardiac magnetic resonance imaging-guided catheterization

The number of centers utilizing cardiac magnetic resonance imaging (CMR)-guided catheterization has increased in recent years [35–39]. These procedures have largely been diagnostic only due to limitations in MRI-compatible devices and catheters. The sequence of the procedure varies but most often entails CMR prior to catheterization. Other institutions begin the procedure in the CCL where access is obtained, followed by a transition to CMR where imaging and RHC are performed. The child is then transferred back to the CCL where any interventions, if needed, can be done [39]. Common populations currently assessed include post-transplant patients and those with PH, cardiomyopathy, and intracardiac shunts.

The rationale for using CMR-guided catheterization is the accuracy of the data obtained and decrease in radiation exposure relative to traditional catheterization. Calculations obtained in the CCL are subject to assumptions and sampling error and are further influenced by the child's underlying anatomy, hemodynamic fluctuations, and the use of oxygen and iNO [35, 40]. CMR avoids many of these confounders and is thus regarded as more precise in calculation of flow and resistance. Other advantages include superior assessment of RV volume, function, and valvar regurgitation relative to other diagnostic modalities and the ability to provide enhanced soft-tissue characterization. Potential benefits to the latter could include improved myocardial biopsy yields and electrophysiology (EP) ablation success, as well as earlier detection of bleeding complications [41–43]. No less importantly, the radiation exposure to the child and providers is reduced. For example, in a child undergoing pre-Fontan evaluation who receives CMR prior to catheterization, the fluoroscopy time needed to obtain pressures and saturations can be eliminated.

These benefits, however, come with an increase in the time that the patient is anesthetized and the introduction of other

risks related to the MRI environment and transfers between CCL and MRI. In a review of their initial experience in patients undergoing MRI-guided right heart catheterization (MRI-RHC), Children's National Medical Center reported that the average anesthetic time for a follow-up transplant biopsy was 2 hours and 56 minutes and for all procedures 3 hours and 24 minutes [39]. Risk in the MRI environment is multifactorial, but the foremost concern is the inadvertent entry of ferromagnetic objects. Protocols that prompt metal screening before the start of catheterization and once again prior to entry into MRI can be preventative [39]. Hemodynamic instability and cardiac arrest during MRI-RHC present additional challenges. Much of the equipment used for resuscitation cannot enter MRI safely, and immediate evacuation of the patient to a different location is indicated. Safe and efficient evacuation is dependent on a well-rehearsed plan that also defines provider's roles in such an event [39]. Patient transfers between CCL and MRI (and back) further add to complexity and provide opportunities for unplanned extubation or loss of vascular access. Nonetheless, many of the above risks can be mitigated with appropriate planning, team awareness, and attention to detail. Of the 72 procedures for MRI-RHC at Children's National, no complications from anesthesia or the MRI-RHC were reported [39].

A rational approach when first planning for these procedures is to over-prepare. Simulation involving all team members is helpful in walking through the sequence of the procedure, identifying problem areas, and determining institutional specific responses to critical events. Radiology can often lead team education regarding MRI risk and also help establish protocols for the safe passage of the patient between CCL and MRI. Interval drills to practice evacuation from MRI in the event of emergencies are recommended. Many programs that set out to do MRI-RHC already have protocols in place for hybrid operating room–MRI suites that can be adapted to the CCL. Patient selection is equally important. Experience first with older and healthier patients can guide subsequent planning on higher risk patients. Anesthetic preparation accounts for setting up MRI as well as the CCL (Table 34.5). Monitors, infusion pumps, and the anesthesia machine within the MRI suite will of course need to be MRI compatible. For patients with PH, an MRI-compatible iNO delivery system is also necessary. Given the complexity and novelty of this procedure, GETA is reasonable, and the threshold for placing dedicated arterial access for blood pressure monitoring may be lower.

Table 34.5 Checklist for anesthetic preparation for CMR-guided catheterization

- ☐ Bag-valve mask and MRI-compatible oxygen tank (for the period of transport between the CL and MRI)
- ☐ Complete check of both the MRI and CL anesthesia machines
- ☐ Circuit extensions added to both
- ☐ Extensions added to intravenous lines
- ☐ Emergency medications drawn and available
- ☐ MRI-compatible infusion pumps and monitors available and functional
- ☐ MRI-compatible iNO machine available and checked (if PH study planned)
- ☐ Plan and roles reviewed for emergency evacuations from MRI

Source: Modified from Deutsch et al. [39].
CLL, indicates catheterization laboratory; CMR, cardiac magnetic resonance; iNO, inhaled nitric oxide; MRI, magnetic resonance imaging; PH, pulmonary hypertension.

KEY POINTS: DIAGNOSTIC CATHETERIZATION

- Anesthetic management can influence the quality of the data obtained during catheterization and can thereby impact clinical decision-making.
- To ensure that the data reflects the child's baseline physiology, variables such as oxygenation, ventilation, and hemodynamics are maintained within the child's usual range during measurement.
- Groups at high risk during diagnostic procedures include neonates and infants, transplant patients in acute rejection or with CAV, those with myocarditis, and patients with systemic-to-suprasystemic PAPs.

Interventional catheterization

The range of interventions offered and the patient types managed in the CCL has broadened significantly in recent years. An overview of common as well as emerging procedures, their anesthetic management, and associated complications are discussed below.

Device closure of cardiovascular communications

Among the most common interventional procedures performed are transcatheter closures of the patent ductus arteriosus (PDA) and certain atrial-level communications such as secundum atrial septal defects (ASDs) and patent foramen ovales (PFOs). Other cardiovascular communications amenable to device closure include muscular VSDs, coronary fistulae, and Fontan fenestrations.

Shared considerations

GETA is used in these cases to minimize patient movement, allow for TEE (ASD and VSD closures), and provide stability in higher risk procedures. This latter group includes the closure of VSDs, preterm PDAs or PDAs in patients with PH, and coronary fistulae. Considerations common to patients undergoing device closure include the need for antibiotic prophylaxis and potential for device embolization (Figure 34.3). Depending on the size of the particular device and where it embolizes, hemodynamic instability can result from obstruction to flow or arrhythmias. Thrombus generation can also lead to stroke in devices lodged within the systemic circulation, thereby necessitating team awareness of the patient's anticoagulation status while attempts at retrieval are made. While most episodes are readily appreciated while still in the CCL, embolization may also occur during the recovery period.

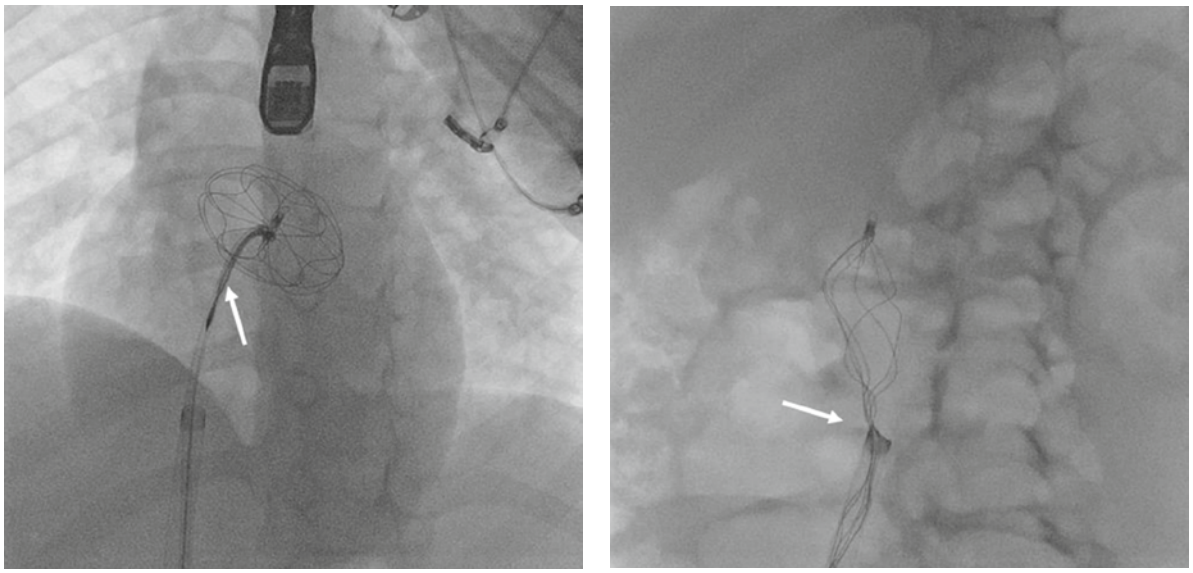


Figure 34.3 (A) A snare (arrow) is used to encircle the device that has embolized into the left atrium. (B) The snare is then used to withdraw the device that is now collapsed (arrow) for removal through the right femoral venous sheath. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

The development of new arrhythmias or changes in hemodynamics should alert one to this possibility. Anesthetic strategies to minimize the risk of delayed embolization include deep extubation (excluding infants or patients otherwise in whom the risk of deep extubation exceeds its benefits), aggressive prophylaxis of postoperative nausea and vomiting (PONV), and extended sedation in the initial recovery period. Dexmedetomidine, morphine, ondansetron, dexamethasone, and/or propofol can be useful agents in achieving these goals, but paramount is communication with the cardiologist to identify those patients at greatest risk. For example, in patients undergoing ASD closure, a large ASD and the presence of multiple deficient rims increase the risk for embolization. If catheter-based retrieval cannot be achieved (e.g., when the device has embolized to the LV and attempts at retrieval may damage the mitral valve apparatus), surgery is indicated.

Atrial septal defects

Complications associated with ASD closure are rare. Apart from embolization (discussed above), the device may encroach upon the atrioventricular (AV) valves or over the ostia of the pulmonary or systemic veins upon release. This risk is minimized by the use of echocardiography to ensure that the veins remain unobstructed and that no new valvular insufficiency or stenosis develops following deployment. Less common are catheter-induced AV block, cardiac perforation, and systemic air embolization (associated with catheter entry into the left heart) [1]. Of note, endovascular and transthoracic echocardiographic (TTE) guidance may occasionally be used rather than TEE to facilitate closure.

The preterm patent ductus arteriosus

Among individuals undergoing PDA closure, preterm neonates and infants pose the greatest challenge due to their associated comorbidities and small size at presentation [44]. Such patients have many of the sequelae of prematurity (intraventricular hemorrhage, bronchopulmonary dysplasia, and a history of necrotizing enterocolitis) and can be as small as 700 g [45]. Due to the increased risk associated with this fragile population, protocols for preparation and the transport of these patients to and from the CCL are necessary (Table 34.6).

Once in the CCL, attention is given to maintaining normothermia and assessing the adequacy of ventilation. Uncuffed endotracheal tubes (ETTs) placed in the neonatal intensive care unit (NICU) usually prohibit accurate $ETCO_2$ monitoring due to associated leaks. Options are to replace the ETT with a cuffed one, or to gauge ventilation by the adequacy of chest rise or $PaCO_2$ via blood gas once femoral venous access is obtained (the femoral artery is avoided due to the potential for leg ischemia with access). Due to issues associated with lung compliance and the inherent limitations of the anesthesia ventilator, a NICU ventilator is used routinely for patients weighing <2 kg. Inadvertent dislodgement of the ETT or IV lines, always a risk in younger patients in the CCL, is a particular concern in this population and mandates communication prior to any movement of the table. Core temperature is measured with an oral esophageal probe, which also serves as a marker for the aortic end of the PDA on fluoroscopy. This gives the interventional team an additional landmark when placing the device (Figure 34.4).

Hemodynamic derangement and desaturations may occur at different points during the procedure. Compression of the chest with the TTE probe can lead to altered ventilation and desaturation (TTE is used in junction with prograde angiography through the venous sheath to assess the PDA and device position before/after release). The catheter used to deploy the device can cause heart block and more commonly can stent open the tricuspid valve. The resulting tricuspid regurgitation (TR) can cause not only hypotension but also

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Table 34.6 Anesthetic management protocol for premature PDA closures

Weight ≤ 2 kg at time of procedure	Weight > 2 kg at time of procedure
Airway and ventilatory management	
1. Trachea intubated by NICU prior to transport	1. Nasal CPAP (if required preprocedure) maintained for transport to the CCL
2. Transport ventilator used for transport	2. Intubation in the CCL by anesthesia
3. NICU ventilator used during the procedure	3. NICU ventilator available if needed. Use of NICU ventilator vs. anesthesia machine at discretion of the anesthesiologist.
4. Staged ventilator weaning over to CPAP in the NICU	4. Staged ventilator weaning over to CPAP in the NICU
Thermoregulation	
1. All patients transported by the NICU transport team in prewarmed incubators to and from the CL	1. All patients transported by the NICU transport team in prewarmed incubators to and from the CL
2. CCL warmed to and kept at 80 °F until draped	2. CCL warmed to and kept at 80 °F until draped
3. Forced air warming used throughout the procedure	3. Forced air warming throughout procedure
Blood	
1. 20 cc/kg blood in the room	1. 1 unit of PRBC, split, in the room
Access	
1. 1 PIV (even if a PICC line is present)	1. 1 PIV (even if a PICC line is present)
Sedation and other medication management	
1. Ketamine, fentanyl, and neuromuscular blockade for intraoperative management	1. Low-dose volatile agent (if anesthesia machine used) with or without ketamine, fentanyl, and neuromuscular blockade for intraoperative management
2. Boluses of vasoactives or initiation of vasoactive infusions at discretion of the anesthesiologist	2. Boluses of vasoactives or initiation of vasoactive infusions at discretion of the anesthesiologist

Source: Modified from Hubbard et al. [44].
CCL, indicates cardiac catheterization laboratory; CPAP, continuous positive airway pressure; F, Fahrenheit; NICU, neonatal intensive care unit; PICC, peripherally inserted central catheter; PIV, peripheral intravenous catheter.

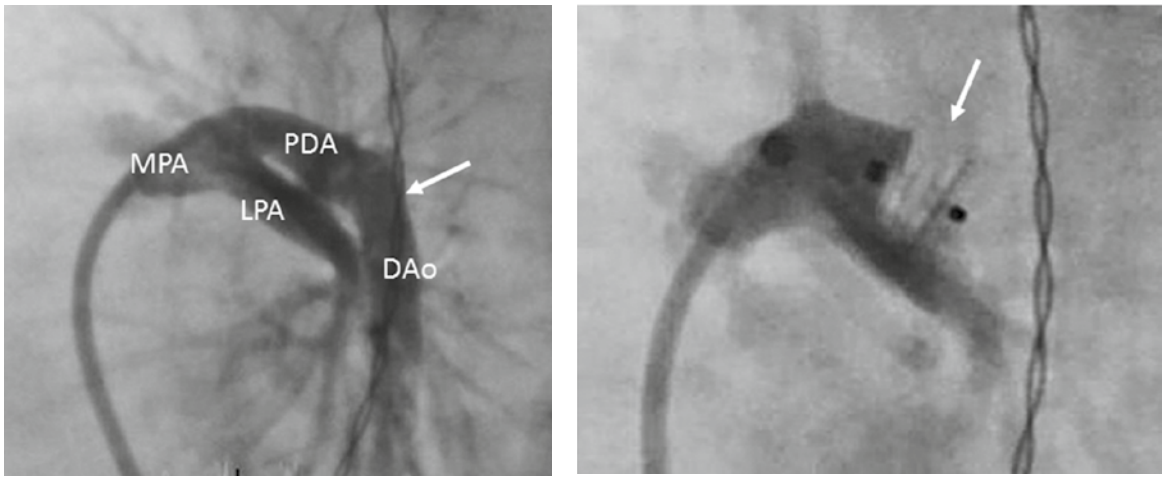


Figure 34.4 Patent ductus arteriosus closure in a premature infant. (A) Anatomy on prograde venous angiography. dAO, descending aorta; LPA, left pulmonary artery; MPA, main pulmonary artery; PDA, patent ductus arteriosus. Note relationship of esophageal temperature probe (arrow) to the dAO. (B) Device occlusion of the PDA. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

desaturation if an atrial communication is present (due to increased right-to-left shunting). Prior to device release, TTE is used to ensure that the device is not protruding into the aorta and causing arch obstruction. Following release, embolization may occur, either into the aorta or, more commonly, into the left PA.

Total IV anesthesia using low-dose ketamine, fentanyl, and muscle relaxant is a commonly used technique in infants weighing <2 kg due to the use of an NICU ventilator. These drugs have the ancillary benefit of promoting hemodynamic stability. For larger and less tenuous preterm infants for whom an anesthesia machine is appropriate, low-dose volatile

agent is often added. Blood and vasoactive agents should be immediately available. Our practice is to leave these patients intubated for return to the NICU.

Ventricular septal defects

Transcatheter closure of VSDs is similarly fraught with the potential for hemodynamic derangements [46]. These can include heart block or tachyarrhythmias, AV valve (AVV) and/or aortic valve regurgitation, volume overload, bleeding, and cardiac arrest. Heart block can develop either secondary to catheter- or device-induced injury. When deployed in proximity to the conduction system, the device's radial force can compress the surrounding tissue. Consequently, attempts at closure of membranous VSDs are associated with a higher incidence of complete heart block (CHB) than muscular VSDs. Though steroids have been administered prophylactically to prevent and subsequently treat device-related CHB (presumptively to decrease inflammation-mediated edema), their use remains speculative [47–50]. Valvular regurgitation can similarly occur due to device deployment near the AV or aortic valve, or separately as a result of catheter-induced trauma. The approach to the VSD, whether retrograde through the left heart or antegrade through the right heart, can cause injury to the aortic valve either alone or both the tricuspid and aortic valves, respectively (Figure 34.5). Notably, recent advancements in delivery systems and softer devices have led to an improved rate of successful closure of various VSDs with lower rates of heart block and arrhythmia [50]. Transcatheter closure of perimembranous VSDs remains controversial, however, due to concerns of heart block, aortic valve injury, and hemolysis associated with residual defects.

Given the prevalence of catheter-induced disturbances, vasoactive support is commonly initiated to provide hemodynamic stability. Adequate peripheral venous access and dedicated arterial monitoring are, therefore, recommended. Transvenous pacing is indicated if heart block persists (and the availability of this equipment should be confirmed prior to starting). Volume overload secondary to flush and contrast administration is common and managed with IV furosemide. Postprocedural disposition can vary depending on the procedure's course, but ensuring the availability of an ICU bed is advisable should continued intubation or pacing be needed.

Coronary artery fistulas

Coronary artery fistulas (CAFs) are anomalous communications between a coronary artery and a chamber of the heart or another blood vessel (Figure 34.6). In the absence of any other cardiac lesion, these fistulas can be a source of pulmonary overcirculation (in patients with fistulas ending in the RV), myocardial ischemia due to coronary steal, or infectious endocarditis. Interventions to close CAFs can be associated with spasm, thrombosis, or dissection of the coronary [51]. Attention to signs of ischemia on EKG and the availability of vasoactive agents to promote coronary vasodilation (nitroglycerin) or hemodynamic support in the event of hypotension (vasopressin, phenylephrine, and epinephrine) are central tenets of anesthetic management. A dedicated arterial line is indicated as the procedure is performed through the femoral arterial sheath. Following occlusion of the fistula, altered flow dynamics that could lead to stasis and thrombosis proximal to the device with subsequent myocardial

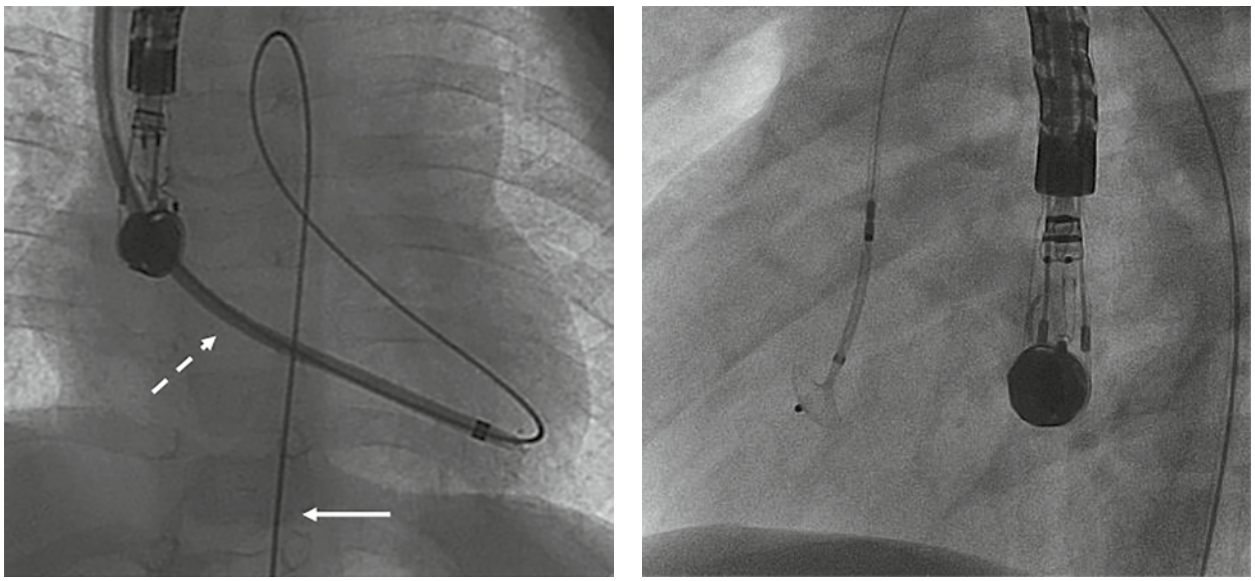


Figure 34.5 Transcatheter ventricular septal defect closure. (A) Antegrade device deployment over an arteriovenous loop. The arterial end of the loop is a wire (arrow) advanced in sequence from the femoral artery through the aortic valve, left ventricle, ventricular septal defect, and into the superior vena cava. The venous end of the loop snares the arterial wire and is externalized through the femoral venous sheath. The delivery sheath (dotted arrow) is then advanced antegrade over the venous end of the loop. (B) Retrograde device deployment entirely from the arterial side. (Source: Morray [50]. Reproduced with permission of Elsevier.)

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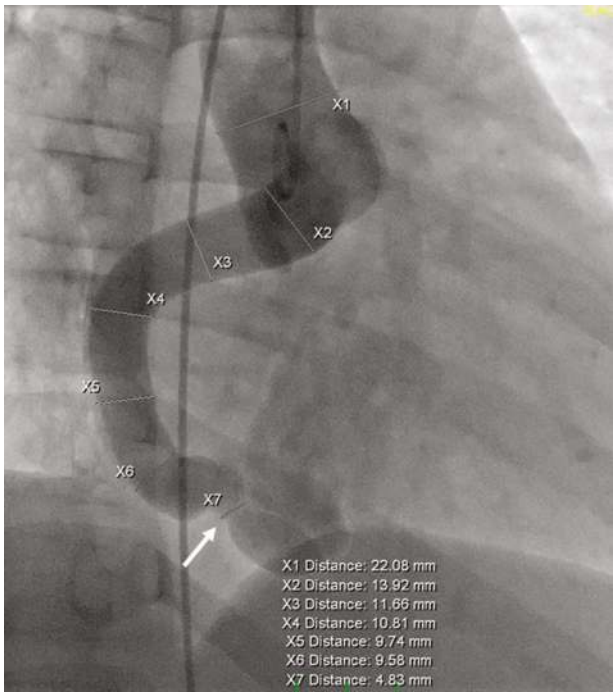


Figure 34.6 Coronary artery fistula. Angiogram demonstrating right coronary artery aneurysmal dilation and continuity with the right ventricle. This 10-year-old child was asymptomatic but had pulmonary overcirculation as a result of the fistula. Device occlusion was targeted at the distal narrowing (arrow). (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

ischemia/infarction necessitate the initiation of anticoagulation and postprocedural monitoring in the ICU. A continuous heparin infusion is commonly initiated prior to departure from the CCL to avoid delays in anticoagulation associated with transfer of care.

Balloon dilation of cardiac valves

Pulmonary valvuloplasty

Children with pulmonary stenosis (PS) can range the spectrum from critically ill neonates to older, otherwise healthy, children. The severity of PS and any associated hypoplasia of the RV and tricuspid valve accounts for these differences in presentation. Neonates whose PS is so severe as to require ductal patency for pulmonary blood flow (PBF) are described as having critical PS [52]. These patients, therefore, have single-ventricle physiology and are managed with prostaglandin (PGE_1) in the periprocedural period. Cyanosis is common in the setting of an atrial-level communication due to the presence of suprasystemic RV pressures, RV diastolic dysfunction, and TR that promote elevated right atrial pressure and right-to-left shunting [53]. The RV is typically hypertrophied with preserved systolic function, but occasionally may demonstrate significant dysfunction. GETA is recommended, and attention to oxygenation and ventilation is necessary to balance $Q_p : Q_s$ in the setting of the patent ductus. Diastolic hypotension is avoided as subendocardial ischemia can develop in the pressure-overloaded RV. During the procedure, because the valve is already severely restrictive and PBF is preserved through the ductus, periods of balloon dilation are well tolerated (Figure 34.7). Major complications such as transient or permanent heart block, tricuspid papillary muscle rupture, balloon rupture, and PA tears are rare [53]. Transient bradycardia or catheter-induced arrhythmias are more common. Postprocedure, PGE_1 may be stopped or continued depending on the size and function of the RV. Importantly, even with the complete relief of obstruction, RV diastolic dysfunction will persist as RV hypertrophy subsides over several months. A gradual wean of PGE_1 may be needed in the ICU to assess the ability of RV to promote PBF. For those demonstrating persistent ductal dependency, either ductal stenting or a surgical shunt is indicated.

Older infants and children presenting for pulmonary valvuloplasty are usually at lower risk. They tend to have a normal-sized RV and tricuspid valve and are able to generate adequate prograde PBF without the need for a PDA. Cyanosis is, therefore, not common but can still occur in the patient with severe obstruction and an ASD. Overarching anesthetic goals include maintaining euvolemia and avoiding hypotension to minimize the risk of ischemia in the thick and pressurized RV. For those rare patients who present with RV dysfunction due to long-standing severe PS, inotropes and vasopressors may be needed to bolster cardiac output and achieve normotension while anesthetized. The process of ballooning causes a transient pause in PBF (in contrast to patients with critical PS) and produces predictable changes in hemodynamics and oxygen saturations depending on whether or not an ASD is present. In patients without an ASD, ballooning is associated with periods of hypotension, bradycardia, and desaturation due to the acute loss of LV filling and PBF. In patients with an ASD, blood pressure is typically preserved during ballooning due to right-to-left shunting across the ASD, but desaturation occurs nonetheless. These events usually self-resolve following balloon deflation, but boluses of phenylephrine may be necessary to treat hypotension in at-risk patients who do not recover within seconds. Preoxygenation prior to ballooning can help minimize the severity of desaturation. Development of severe infundibular obstruction after ballooning, although rare, has been reported [54–56]. Adequate preload and a slower heart rate can ensure ventricular filling in these cases. Beta-blockade is rarely necessary. Although this procedure can be performed with sedation in the compensated child or adolescent, the variable length of the procedure and the significant stimulation associated with ballooning lead us to use GETA. If uneventful, patients are commonly discharged on the same day.

Further along the continuum of PS is pulmonary atresia with intact ventricular septum (PA/IVS). As with critical PS, this lesion is ductal dependent for PBF, and decompression of the RV is sought to establish prograde PBF that may allow for a future biventricular or 1 ½ ventricle repair. These patients, however, may have abnormalities in their coronary anatomy that preclude RV decompression. The pressurized RV can result in the formation of fistulous connections between the RV and the epicardial coronary arteries, and when combined with proximal coronary stenosis or occlusion (present in 9–34% of patients with PA/IVS)[57], an RV-dependent coronary circulation (RV-DCC) results [58] (Figure 34.8). Decompression of the RV in this setting would lead to

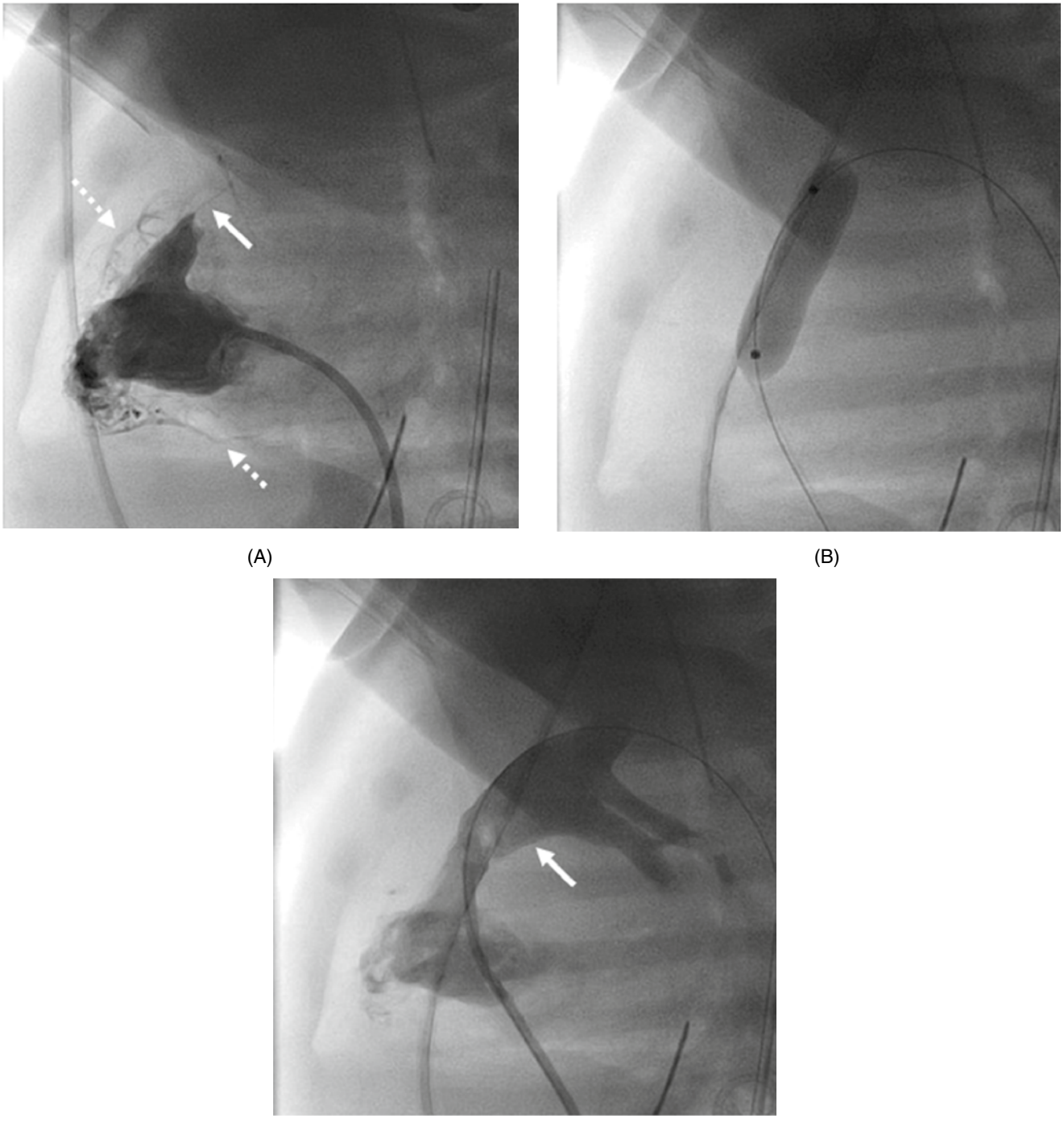


Figure 34.7 Balloon valvuloplasty in critical pulmonary stenosis. (A) Right ventricular (RV) angiogram in a neonate with critical pulmonary stenosis. A very thin jet of antegrade flow can be seen across the pulmonary valve (arrow). Also noted is filling of the coronary arteries (dotted arrows) via fistulous connections (non-RV dependent in this case). (B) The pulmonary valve was crossed with a fine wire and dilated with a balloon. (C) After pulmonary valvuloplasty, there is a wide jet of antegrade flow (arrow) across the pulmonary valve. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

myocardial infarction. Consequently, the first procedure undertaken in the CCL is a diagnostic coronary and RV angiogram to rule out the presence of RV-DCC. For patients without RV-DCC, RV decompression and prograde PBF can be established with wire or radiofrequency (RF) perforation, followed by ballooning of the atretic valve. Given these additional steps, the duration of the procedure is longer and the risks of complications greater than with balloon valvuloplasty alone. Risks can include heart block, right heart perforation, tamponade, volume overload, dilutional anemia, and

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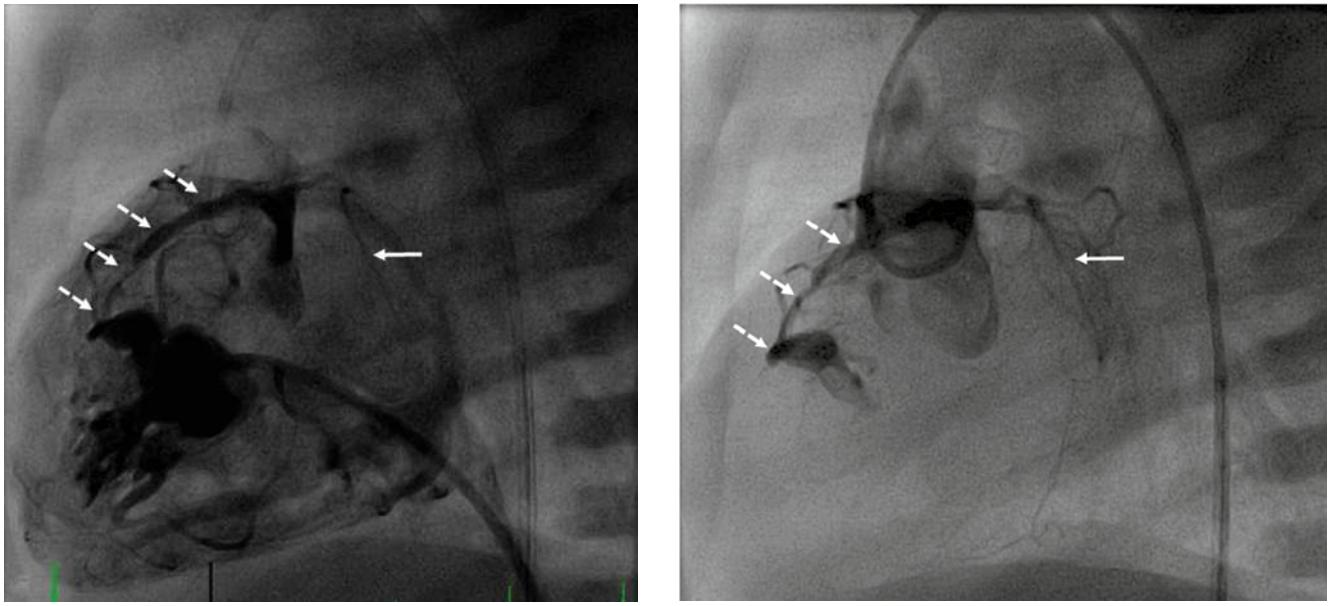


Figure 34.8 Right ventricle (RV)-dependent coronary circulation. (A) RV angiogram in a newborn with PA-IVS. Interruption of the mid-left anterior descending coronary artery (dotted arrows) with a fistulous connection to the RV is seen. A small circumflex coronary artery (solid arrow) is also seen. (B) Direct angiography in the left main coronary artery confirms interruption of the left anterior descending coronary artery (dotted arrows) and a small circumflex coronary artery (solid arrow). (Source: Cabrera et al. [58]. Reproduced with permission of Elsevier.)

acid–base derangement [59, 60]. Ductal stenting may be performed in the same setting or at a later date (see PDA stenting to augment PBF). Timing is often dependent on the size of the ductus and stability of the patient following what may be a lengthy intervention at the atretic valve [61].

Aortic valvuloplasty

As with PS, valvular aortic stenosis (AS) can manifest variably depending on the severity of the obstruction and any associated cardiac lesions. Critical AS is the most severe manifestation and presents in the neonatal period as a lesion that is ductal dependent for systemic blood flow. Definitive treatment entails relieving the valvular obstruction. Medical management prior to arrival in the CCL includes the initiation of PGE_1, and in the subset of patients with compromised end-organ perfusion and respiratory failure, inotropic support, and mechanical ventilation [62]. Of note, hemodynamic and respiratory status should be regarded as tenuous even in the neonate presenting on room air and PGE_1 alone. The LV is most commonly dilated and dysfunctional at baseline, and the procedure may further exacerbate hemodynamics due to catheter-induced arrhythmias, decreases in cardiac output with ballooning, and the potential for new aortic insufficiency following valvuloplasty. GETA is, therefore, used. An infusion of epinephrine is often started with induction of anesthesia if the patient is not already receiving it, and vasopressin may be indicated to optimize coronary perfusion pressure. Due to the risk of arrhythmias, defibrillation pads should be immediately available.

The vascular access approach planned by the cardiologist can provide additional insight into specific risks as well as the duration of the procedure. The carotid approach offers the most direct and expedient route to the aortic valve but can be associated with neurologic injury. It is, therefore, reserved for the smallest of neonates for whom the risk of femoral artery injury is thought to exceed that of the carotid [63–65]. To facilitate carotid access, the cardiologist may request that the patient be turned 180° away from the usual position (such that the airway is furthest from the anesthesiologist). Care with positioning of lines and the ETT is necessary in this circumstance to minimize the risk of line displacement or kinking of the ETT. A more common approach to the aortic valve is retrograde through the femoral artery. Antegrade approaches through the femoral vein (and then in sequence through the atrial septum, mitral valve, and LV) are less common due to the instability associated with passing the catheter through potentially smaller left-sided structures (with risks of arrhythmia, mitral valve damage, and perforation) [59]. If the femoral artery is used, additional arterial access for blood pressure monitoring is indicated. New, hemodynamically significant aortic insufficiency following ballooning (indicated by diastolic hypotension and ischemic ST changes) requires urgent surgical intervention for valve repair/replacement.

Management of reinterventions later in life, or first-time interventions in older children or adolescents, is marked by the usual concern of maintaining an adequate coronary perfusion [62]. Anesthetic technique and risk assessment can be guided by the patient's age, LV function, severity of the gradient, and comorbidities. For older patients who have a borderline indication for intervention based on Doppler-derived mean transvalvular gradients, the peak-to-peak gradient obtained during catheterization can provide definitive information to direct therapy. In such cases, light sedation may be preferable to general anesthesia during the diagnostic portion since the latter

may lead to an underestimation of the actual gradient. Our preference otherwise is to use GETA to avoid the risk of movement with balloon dilation that may increase the risk of aortic valve injury. Importantly, rapid RV pacing may be used to reduce stroke volume and minimize balloon movement during inflation in older patients. The resulting decrease in cardiac output is typically well tolerated in those with preserved LV function but may necessitate treatment with phenylephrine to expedite recovery. As the approach to the aortic valve will most commonly be through the femoral artery, the need for a separate arterial line for dedicated blood pressure monitoring is dictated by the patient's baseline LV function.

Balloon angioplasty and/or stent placement

Pulmonary arteries

A number of pathologies are associated with PA stenosis, including syndromes such as Alagille or Williams-Beuren and different forms of CHD in which stenosis can develop either independently or as a consequence of surgery (ductal origin of the PA, palliated single ventricles, Tetralogy of Fallot (TOF), truncus arteriosus, and transposition, among others).

Similar to valvular PS, anesthetic management in children with PA stenosis is dependent on the degree of stenosis present and its effects on RV pressure and function. Estimates of RV pressure can be gauged by the presence of a TR jet and compensatory RV hypertrophy on echocardiography. Euvolemia and age-appropriate diastolic perfusion pressures should be maintained to decrease the risk of ischemia. Catheter-induced arrhythmias and periodic hypotension (due to TR caused by catheters en route to the PAs) are common, particularly in younger patients. Though well tolerated in children with preserved ventricular function, those with depressed function may need vasoactive support.

Critical events associated with PA angioplasty/stenting include hemorrhage due to vessel rupture, lung reperfusion injury, and occlusion of the left mainstem bronchus with stenting of the left PA [1, 66–69]. The potential for life-threatening hemorrhage, though rare with the introduction of covered stents and vessel occlusion, requires the presence of large-bore IV access and packed red blood cells in the CCL. Lung reperfusion injury is more common, with a reported incidence of 15–22% in published cohorts (higher when segmental and subsegmental branches with severe stenoses are involved) [69, 70]. This presents as a decrease in both lung compliance and PaO_2 : FiO_2, and occasionally with blood-tinged fluid in the ETT. Proposed mechanisms include an acute increase in hydrostatic pressure due to increased flow following angioplasty or the acute increase in LV end-diastolic volume in a noncompliant LV. Treatment entails conservative management with continued mechanical ventilation, increased positive end-expiratory pressure (PEEP), and diuresis if oxygenation and ventilation are compromised. Rarely, one lung ventilation is needed. In patients at high risk for developing hemorrhage or reperfusion injury, we have occasionally placed a bronchial blocker preemptively (Figure 34.9). The potential for acute left bronchial compression should be considered in the setting of a recently deployed left PA stent with a new finding of diminished lung compliance and left lung atelectasis (assessed via fluoroscopy) [67]. Bronchoscopy can be used to confirm this diagnosis.

Additional risk can be inferred based on patient characteristics. Patients with Alagille and Williams-Beuren syndromes may present for PA intervention and carry comorbidities unique to each condition – namely, the risk of liver disease and coincident supravalvar AS, respectively [71]. Moreover, those with a history of D-transposition of the great arteries (d-TGA) status post the arterial switch operation may be at risk for coronary compression with attempts at branch PA stenting. The LeCompte maneuver in these patients can place the branch PAs in proximity to the translocated coronaries, and so testing is done to assess for coronary compromise prior to stenting [72]. The presence of profound hypotension and/or ST changes on EKG with testing also suggests the need to abort.

Pulmonary veins

Pulmonary vein stenosis (PVS) in children can be a relentless disease associated with significant morbidity and mortality [73–75]. Classified as either primary (congenital) or postrepair (acquired), the pathophysiology of PVS is an increase in pulmonary venous pressure that can lead to PH, right heart failure, and, ultimately, death [76–79]. Characteristics associated with increased mortality include earlier age at presentation, bilateral disease, multivessel involvement, and the concurrent presence of CHD and/or prematurity [80–82]. The foundation of management is early surgical or catheter-based therapy to relieve the stenosis followed by repeat catheterizations as indicated to address disease recurrence and/or progression (Figure 34.10).

Due to the risk of RV failure secondary to PH, preanesthetic evaluation focuses on the RV and signs of systemic or suprasystemic PAPs [73]. For those entering the procedure with depressed RV function, preparations to support the RV

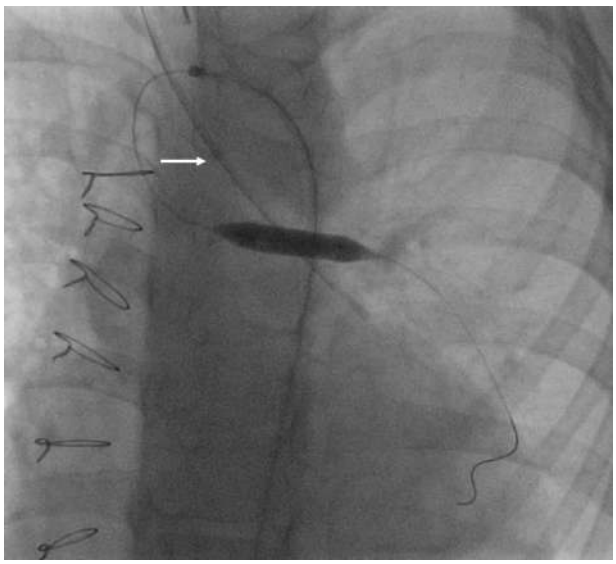


Figure 34.9 Bronchial blocker with pulmonary artery angioplasty. A left bronchial blocker (arrow) has been inserted prophylactically to contain hemorrhage in a 7-year-old child with PA/VSD/MAPCAs undergoing pulmonary artery angioplasty. An angioplasty balloon is seen inflated in the left pulmonary artery. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

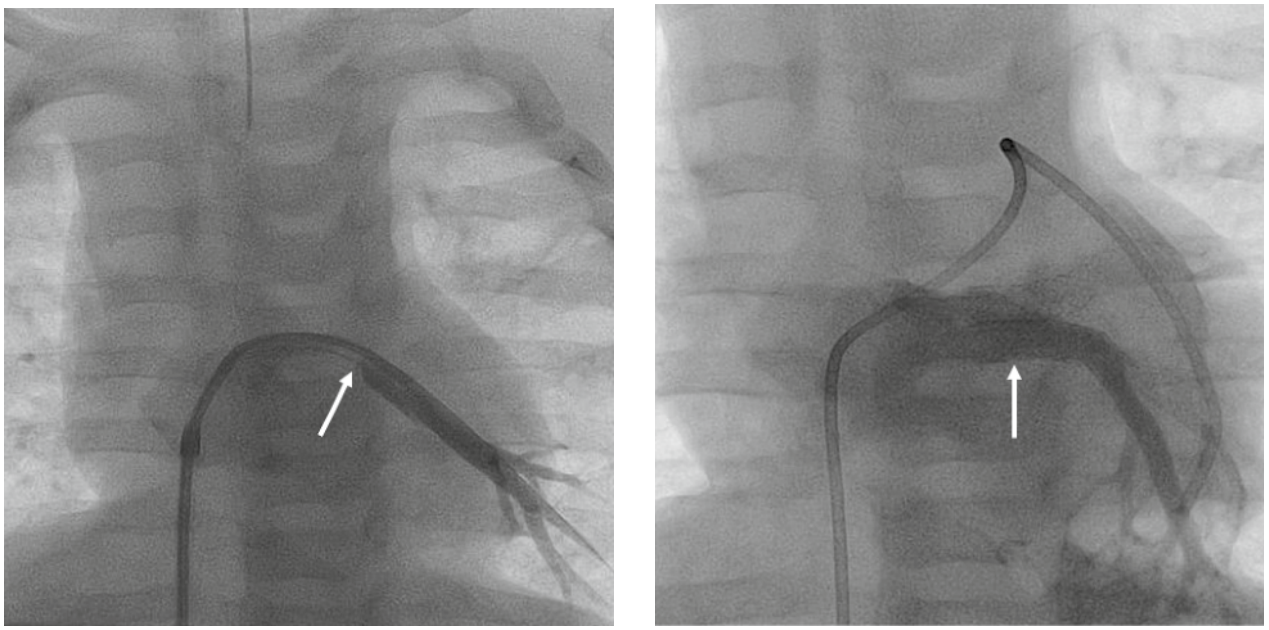


Figure 34.10 Pulmonary vein stenosis angioplasty and stenting. (A) Severe left lower pulmonary vein stenosis (arrow) can be seen in a 1-year-old. (B) After left lower pulmonary vein stenting (arrow), a left lower pulmonary artery wedge injection shows an unobstructed left lower pulmonary vein. Also noted is a stent in the left upper pulmonary vein. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

should include the availability of epinephrine, phenylephrine, vasopressin, iNO, and, in the highest risk patients, ECMO. Consideration should be given to starting epinephrine and vasopressin prior to induction in those with moderately to severely depressed function. Though counterintuitive that a pulmonary vasodilator would be useful in patients with a downstream obstruction, some patients with PVS may respond to iNO with a significant reduction in PAP [83]. Its use may be considered if acute reductions in pulmonary afterload are needed (and can be stopped quickly if the patient deteriorates with its initiation).

Preprocedural respiratory status can also indicate disease severity and is related to the number of veins involved and the degree of stenosis. Children presenting in respiratory distress due to pulmonary venous congestion may be tachypneic with retractions and in need of noninvasive ventilatory support or intubation. Even in the absence of RV dysfunction, such signs indicate limited reserve and the potential for instability with anesthetic induction and maintenance. Because lung compliance, oxygenation, and ventilation can all worsen during the procedure (as discussed below), patients already starting with pulmonary edema may demonstrate less tolerance for additional insults than those without it. Preemptive diuresis with IV furosemide (1 mg/kg) is often used in at-risk children (and can be re-dosed as indicated).

Procedural risk and duration can otherwise be gauged by the number of veins needing intervention, whether an ASD is present, and if the femoral veins are patent. Multivessel PVS is associated with both a longer intervention and an increased risk of instability. The latter is related to the potential for pulmonary edema and hemorrhage that increases incrementally with each vein requiring intervention. In the absence of an ASD, transseptal puncture or RF perforation is needed to pass through the atrial septum to access the pulmonary veins. Though generally safe, this added step confers the risk of cardiac perforation while also increasing overall procedural time. Stenotic or thrombosed femoral veins can present another challenge to the interventionalist. Recurring use of the femoral veins with repeat interventions can render them inaccessible. Transhepatic venous access may be needed, which also carries a higher risk of bleeding and AV block [84]. A review of prior anesthetics in patients presenting for repeat intervention can often provide insight into the need for these additional procedures and general information regarding how the anesthetics and interventions were tolerated.

The previously alluded to complications of pulmonary edema and pulmonary hemorrhage can be anticipated in children with severely stenotic veins. Patients without any prior intervention and evidence of significant disease are at the highest risk. Pulmonary edema can present either gradually with fluid overload related to flush and contrast administration or more acutely with the transient occlusion of a pulmonary vein during angioplasty and stenting. The latter can also cause pulmonary hemorrhage. Balloon inflation in such settings can be associated with an acute increase in pulmonary venous pressure that can lead to airway bleeding. More common, however, is pulmonary hemorrhage in the setting of a PA wedge injection (used to define pulmonary venous anatomy). Injections into lung segments that are drained by nearly occlusive veins will result in markedly increased capillary pressures (Figure 34.11). Such bleeding is usually self-limited with subtle changes in compliance but can manifest as gross blood in the ETT or an acute decrease in lung compliance followed by profound desaturation. As

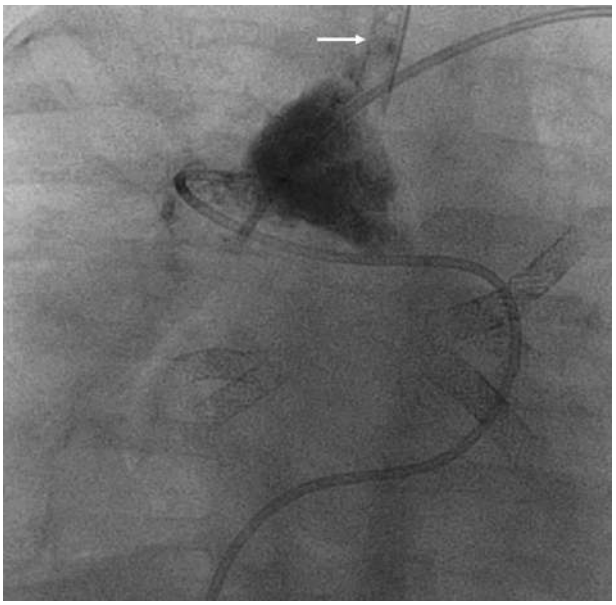


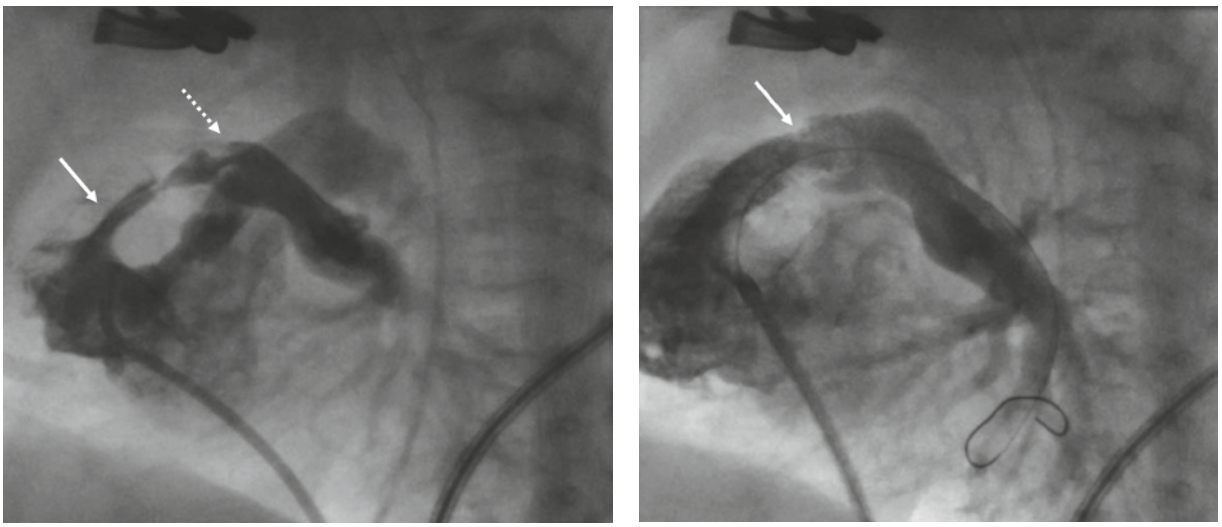
Figure 34.11 Pulmonary hemorrhage with pulmonary artery wedge injection in pulmonary vein stenosis. Right upper pulmonary artery wedge angiogram in a child with an obstructed right upper pulmonary vein. Contrast is seen entering the right bronchus and trachea (arrow). Stents can be also noted in multiple affected pulmonary veins. A peripherally inserted central catheter is also seen entering from the left arm. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

with the management of reperfusion injury, pulmonary hemorrhage can be treated conservatively with suctioning, continued mechanical ventilation, diuresis, and increased PEEP and FiO_2. In severe or persistent cases, endotracheal instillation of tranexamic acid can be efficacious [85]. The need for ECMO is rare, but indicated if hypoxemia is not reversible and contributing to hemodynamic instability. Of note, episodes of either pulmonary hemorrhage or edema that require escalations in hemodynamic and/or ventilatory support should prompt a discussion of whether or not to proceed. If some of the stenotic veins have already been addressed, a reasonable strategy is to return to the CCL once the patient has recovered. If no intervention has yet been performed in the setting of severe, multivessel disease, ECMO cannulation may be needed prior to proceeding.

Right ventricular outflow tract stenting

Stenting of the right ventricular outflow tract (RVOT) has gained acceptance as an alternative to the modified Blalock–Taussig shunt (mBTS) in the initial palliation of premature or severely cyanotic infants with TOF (Figure 34.12). In a single-center review comparing RVOT stenting to the mBTS, patients undergoing RVOT stenting were found to have a shorter hospital length of stay, improved PA growth, and comparable mortality while awaiting complete repair [86].

Common anesthetic concerns in this population include the potential for hypercyanotic episodes, or "tet spells," prior to stent placement, and the presence of significant noncardiac comorbidities that may influence anesthetic planning. The usual measures taken to prevent a hypercyanotic episode should be employed, such as euvolemia, adequate anesthetic depth, and avoidance of decreases in SVR. In patients who are cyanotic, transfusion to a hematocrit >40% can serve the purpose of providing preload while also increasing oxygen delivery and SVR. FiO_2 can be increased as needed. Catheter-induced arrhythmias or TR can precipitate hypotension and are treated with boluses of phenylephrine or the initiation of a vasopressin infusion. TR can also cause systemic desaturation in the setting of an ASD due to increased right-to-left shunting. Transient desaturation can be anticipated with balloon inflation and preemptively



(A) (B)

Figure 34.12 Right ventricular outflow tract stenting in Tetralogy of Fallot. (A) Severe right ventricular outflow tract obstruction (arrow) in an infant with Tetralogy of Fallot with hypercyanotic spells. Also noted is severe valvar pulmonary stenosis (dotted arrow). (B) After right ventricular outflow tract stenting (pulmonary valve annulus intentionally crossed), there is significant improvement in antegrade flow across the right ventricular outflow tract and pulmonary valve. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

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managed with phenylephrine and preoxygenation. Because RVOT stenting may constitute definitive therapy in those infants for whom operative risk is prohibitive [87], an awareness of the child's noncardiac risk factors and how they may influence anesthetic management is critical. Such patients may also present for reintervention in the setting of in-stent stenosis and remain at-risk for hypercyanotic episodes until the stenosis is relieved.

Procedural risks include perforation of the PA or RVOT, pulmonary edema, tricuspid valve regurgitation, and stent embolization [86]. Perforation of the RVOT can manifest as a pericardial effusion, whereas puncture of the PA can present as hemoptysis or the appearance of contrast in the pleural spaces or lung fields [73]. Significant pericardial effusions require drain placement. Blood drained from the pericardium may be directly transfused back to the patient if the volume is needed. Protamine can be used to reverse anticoagulation in this setting if the activated clotting time (ACT) is prolonged, and surgery may be necessary if bleeding persists. Pulmonary edema develops most often as a result of reperfusion injury following relief of the obstruction to PBF. Treatment is conservative with continued mechanical ventilation, increased PEEP, and diuresis.

Coarctation of the aorta

Catheter-based management of coarctation of the aorta (CoA) entails balloon angioplasty with or without stent placement. Patient size and age dictate which approach is used. Angioplasty alone is typically reserved for neonates and infants, whereas combined angioplasty and stenting is used in older patients [88]. Common indications for catheter-based management include the initial treatment of discrete coarctation in older children and adolescents and reintervention in those presenting with discrete recurrent or residual coarctation (Figure 34.13).

Anesthetic management of CoA varies with patient age and clinical status (i.e., ventricular function) [88]. Sedation has been used successfully in older children and adolescents, but a deep level is required to blunt the noxious stimulus of aortic ballooning. Our practice is to use GETA regardless of patient age or ventricular function to reduce the movement-associated risks of aortic dissection or stent migration.

Common aspects of care include the need for large-bore IV access and blood pressure monitoring in the right upper extremity (RUE). Assuming a left aortic arch with normal branching, the RUE blood pressure reflects both cerebral and coronary pressures (as the innominate artery arises precoarctation). In contrast, a lower extremity or left upper extremity blood pressure would underestimate these values and lead to unnecessary treatment if used. Additional arterial access beyond that placed by the interventionalist is usually unnecessary but may be indicated based on individual patient risk and need for postprocedural monitoring (e.g., infants with severely depressed LV function undergoing angioplasty as a temporizing procedure or for recurrent CoA following stage 1 palliation). Of note, the arterial access placed by the interventionalist is most often at the femoral artery but can include the carotid or axillary arteries in smaller patients (<2 kg) to avoid femoral artery injury. In older patients, rapid RV pacing may be used when stenting is planned to minimize the risk of migration with deployment and is well tolerated in those with preserved LV function. Postprocedural disposition is guided by preprocedural clinical status. For most undergoing elective intervention, neither ICU admission nor IV antihypertensives are needed.

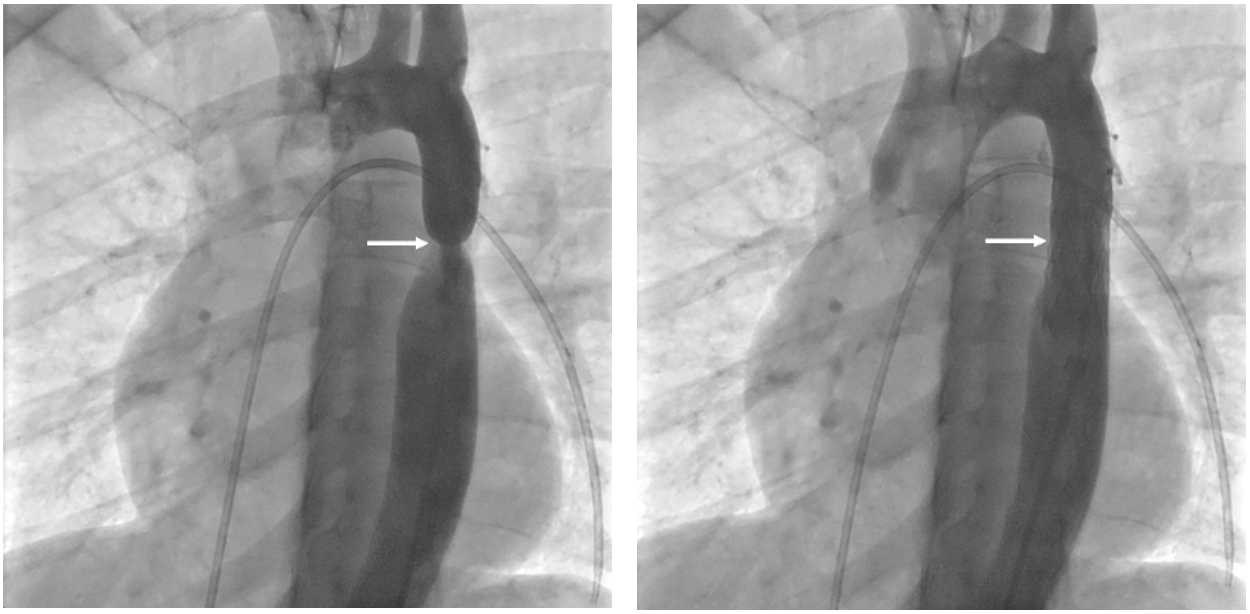


Figure 34.13 Coarctation of the aorta angioplasty and stenting. (A) Severe native coarctation of aorta (arrow) in an 18-year-old adolescent. (B) After bare metal stent implantation (arrow) from a femoral arterial approach, there is unobstructed flow in the descending aorta. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

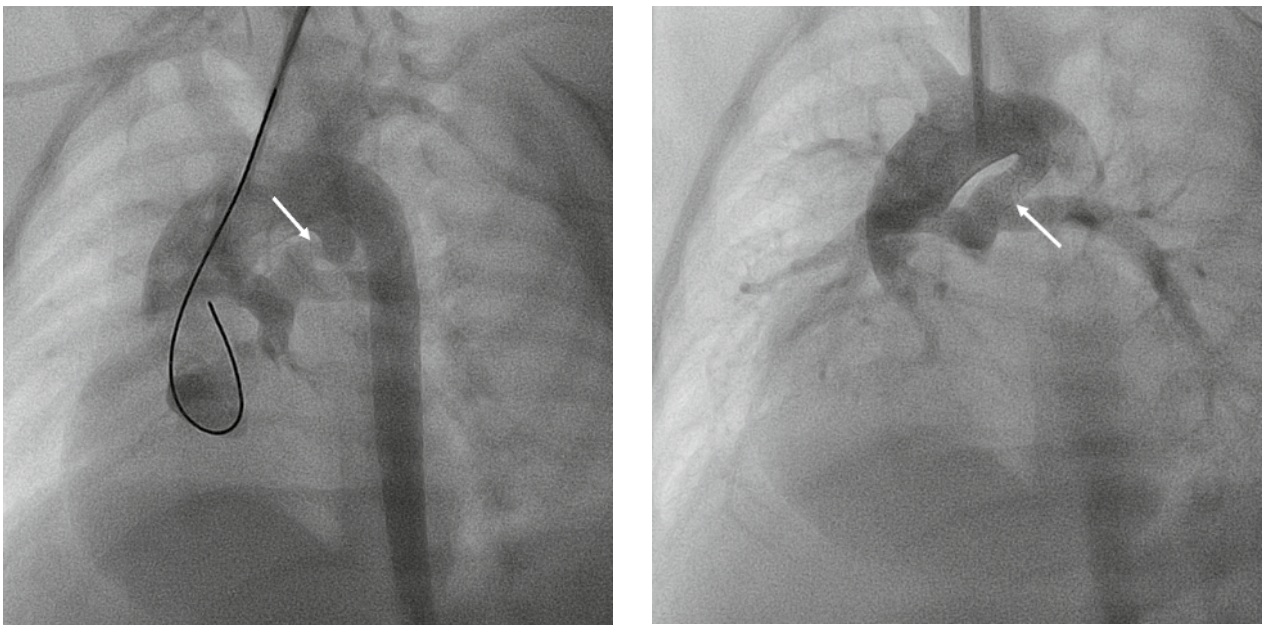
Acute complications include vessel dissection or disruption, cerebrovascular accidents, stent migration, and balloon rupture [89, 90]. Patients weighing <30 kg presenting for stenting should raise concern for the potential for access site injury. The sheath size necessary to deliver the stent can approximate the size of the femoral or iliac arteries themselves, thereby increasing the risk of vascular disruption with both sheath placement and withdrawal. Acute hypotension unrelated to pacing or ballooning should elicit evaluation for contrast extravasation. Temporary balloon inflation and subsequent covered stent placement are used to temporize in such situations. The risks of both aortic dissection and cerebrovascular accidents appear higher with older age, with patients over 40 years of age at greatest risk [90]. Aneurysm formation at the site of intervention is a late complication more associated with angioplasty alone than stenting.

Patent ductus arteriosus stenting to augment pulmonary blood flow

Ductal stents have been used increasingly in recent years in the initial palliation of neonates with ductal-dependent PBF (Figure 34.14). Data comparing ductal stenting to the mBTS have demonstrated comparable outcomes in terms of death and unplanned reintervention to address cyanosis [91]. Children receiving ductal stents have decreased lengths of stay in the ICU, lower procedural complications, and larger and more symmetric PAs at the next stage of palliation relative to those managed with a mBTS [88]. These positives are balanced, however, by an increased need for subsequent reintervention and a higher initial failure rate due to an inability to stent the duct [91, 92]. This latter concern and the unique complications that may occur during the procedure are of interest to the anesthesiologist.

PGE_1 can be either continued or stopped in preparation for ductal stenting. If continued, there may be concern that the PDA is tortuous and at risk for spasm with manipulation. More commonly, PGE_1 is stopped hours prior to the procedure [1]. This is to produce a reduction in ductal diameter that allows the stent to be well anchored on release, thereby decreasing the risk of embolization. Ductal narrowing is clinically apparent when the patient begins to desaturate. The time interval between stopping PGE_1 and the onset of desaturation, often known to the ICU through previous trial and error, can inform scheduling as well as guide urgency. The ideal situation would be to have the child positioned and prepped in the CCL before severe desaturation occurs. In the event of such desaturation, PGE_1 can be restarted (patients who are entirely ductal dependent are particularly vulnerable). For those with an ancillary source of PBF (e.g., PS or PA/IVS following RF perforation and dilation), an alternative strategy can be to start vasoactives to augment PBF while the procedure proceeds urgently.

The duct can be approached from a variety of access points dictated by its location on the aorta [93]. The particular approach used influences patient positioning and any additional monitoring that may be needed. Patients with a percutaneous carotid or axillary approach may require positioning such that the airway is directed 180 degrees away from the anesthesiologist (called the "flip technique") [94]. Care in securing the ETT, IVs, and monitoring lines is essential as patient access is limited in this position.



(A) (B)

Figure 34.14 Ductal stent for pulmonary blood flow. (A) A tortuous ductus arteriosus (arrow) can be seen supplying confluent branch pulmonary arteries in a neonate with ductal-dependent pulmonary blood flow. Also noted is a percutaneously placed left common carotid artery sheath. (B) A ductal stent is seen (arrow) that has been placed via a percutaneous left common carotid artery approach. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

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Beyond standard monitoring, placement of an additional arterial line is often indicated. Because the arterial access obtained by the interventionalist may be used for deploying the stent, a separate arterial line is needed to provide accurate blood pressure monitoring and blood gas assessment both during and after the procedure. The location of the duct and the interventionalist's approach can guide where to place this line. For example, in a patient undergoing a left axillary artery approach, a left radial arterial line (and the pulse oximeter on that hand) would be blunted. In the absence of central venous access, two peripheral IVs are placed: one to allow for volume resuscitation and bolus drug administration and the other for continuous infusions of vasoactives. It is the norm at our institution to initiate vasoactives during this procedure, whether with epinephrine, vasopressin, or both. For patients undergoing a common carotid approach, cerebral near-infrared spectroscopy (NIRS) on the side being accessed may be useful to detect changes in perfusion [95]. A Foley catheter is routinely placed. Other concerns common to the neonatal population include maintaining normothermia and normoglycemia. A forced air warmer and the use of a dextrose-containing carrier fluid can address these issues.

Critical events that may occur with manipulation of the ductus include ductal spasm and thrombosis. In patients who are ductal dependent, either event can lead to life-threatening hypoxia. Boluses of epinephrine (1–10 mcg/kg) can support hemodynamics while attempts are made to open the ductus, and in the case of spasm, PGE_1 can be reinitiated at high dose (0.1 mcg/kg/min) or given as a bolus (0.1 mcg/kg). PGE_1 should, therefore, always be immediately available. Thrombosis can be managed additionally with a bolus of heparin (100 units/kg). Preparations for ECMO are made if attempts at restoring ductal patency are not rapidly successful. Even in cases when ductal spasm does not obviously occur, passage of the wire through the ductus can also promote desaturation. FiO_2 is increased in anticipation of this event, and vasoactives are titrated to optimize PBF. Other intraprocedural complications of note include dissection and stent embolization [1, 93]. The latter may prove difficult to retrieve and can adversely affect systemic blood flow or PBF. Following successful stenting, oxygen saturations should improve. Attention is then shifted to minimizing the risk of overcirculation by titrating down on FiO_2 and vasoactive support as able. Patients are most often kept intubated following the procedure to allow for further stabilization and optimization prior to extubation. Prior to leaving the CCL, perfusion to the extremity used for access is evaluated. If there are any concerns for inadequate pulses or a cool extremity, a heparin infusion is started. Further discussion of ductal stenting is presented in Chapter 19.

Creation of cardiovascular communications

Balloon atrial septostomy

Balloon atrial septostomy (BAS) is indicated in those forms of CHD that require an unrestrictive atrial septal communication. Examples include d-TGA (to improve systemic saturations through better mixing), hypoplastic left syndrome (to relieve left atrial hypertension), or tricuspid atresia, total anomalous pulmonary venous return, or severe PS/atresia (to off-load the right heart and augment cardiac output).

The procedure is performed through either umbilical or femoral vein access and, in the case of d-TGA, can often be done at the bedside with TTE guidance. Once the balloon catheter is positioned in the left atrium, the balloon is inflated and a forceful jerk is applied to bring the balloon back to the right atrial–inferior vena cava junction [1]. This is repeated as needed to achieve an unrestrictive atrial communication. A subset of patients with thicker atrial septae for whom a BAS alone would be ineffective include neonates with hypoplastic left heart and infants older than 4–6 weeks. An atrial communication in these children is created using RF perforation or blade atrial septostomy, followed by ballooning and/or stenting of the atrial septum. Given the increased complexity of this group and need for fluoroscopy, these procedures are performed in the CCL.

Different anesthetic techniques can be used in the stable neonate undergoing BAS. Our approach is to intubate using low-dose fentanyl (and/or ketamine) and muscle relaxant, and in those with an uncomplicated preprocedural and intraprocedural course, to extubate following successful ballooning. Those who are critically ill beforehand, such as the hypoplastic left heart syndrome (HLHS) patient with a highly restrictive atrial septum, are often already intubated and receiving significant inotropic and ventilatory support. Management is supportive until the atrial septum is opened. Thereafter, oxygen saturations should increase but can occur at the expense of systemic perfusion. Acute hemodynamic instability can result with the increase in Qp and loading of the RV.

Procedural complications are rare but can include balloon rupture and embolization of balloon fragments, stent embolization (if an atrial septal stent is used), vascular injury including avulsion of the pulmonary vein or inferior vena cava, or cardiac injury or perforation [1]. Examples of the latter are mitral valve injury with distal placement of the balloon, or rupture of the atrial appendage.

Palliation in pulmonary hypertension

In the child with worsening PH who is unresponsive to medical therapy, catheter-based options for decompressing the RV and pulmonary vasculature include atrial septostomy/stenting, PDA stenting, and the reversed Potts shunt (left PA to descending aorta). While these procedures result in desaturation due to right-to-left shunting, they differ in the end organs affected [15]. With atrial septostomy, all end organs (including the brain and myocardium) are subject to desaturated blood. In contrast, the PDA stent and reversed Potts shunt deliver deoxygenated blood only to the splanchnic and lower extremity circulations (while preserving oxygenated blood flow to the brain and heart). Additional benefits over an ASD include a decrease in RV afterload, with a subsequent improvement in LV performance through a more normalized position of the interventricular septum. The reversed Potts shunt can be achieved via either ductal stenting in those infants and young children who have a still persistent PDA or the *de novo* creation of a left PA–descending aorta connection. The latter is achieved using RF perforation and the placement of a covered stent [96]. Concerns for both techniques include the risk of too large a shunt: decreased PBF with subsequent hypoperfusion of the brain and heart (due to decreased LV filling) and severe lower extremity

desaturation. Alternatively, blood flow from the aorta may be siphoned into the pulmonary circulation when PAP is subsystemic. One-way valves have been used to address this [97]. Such patients are clearly among the highest risk for hemodynamic decompensation. Established strategies for the anesthetic management of severe PH apply.

Fontan fenestration creation

Children with the Fontan circulation may need a fenestration in the setting of worsening systemic venous hypertension (presenting clinically as protein-losing enteropathy or persistent pleural effusions) or to achieve intracardiac access for arrhythmia ablation. An opening is most often created using a combination of needle/RF perforation and ballooning (with or without stenting), fluoroscopy, and echocardiography. Procedural risks include bleeding with pericardial effusion or tamponade, systemic embolization of air or thrombus, and volume overload with lengthy attempts at conduit perforation. Anesthetic risk is associated with the underlying Fontan physiology and the negative effects of PPV (on venous return) and anesthesia (on SVR and venous capacitance).

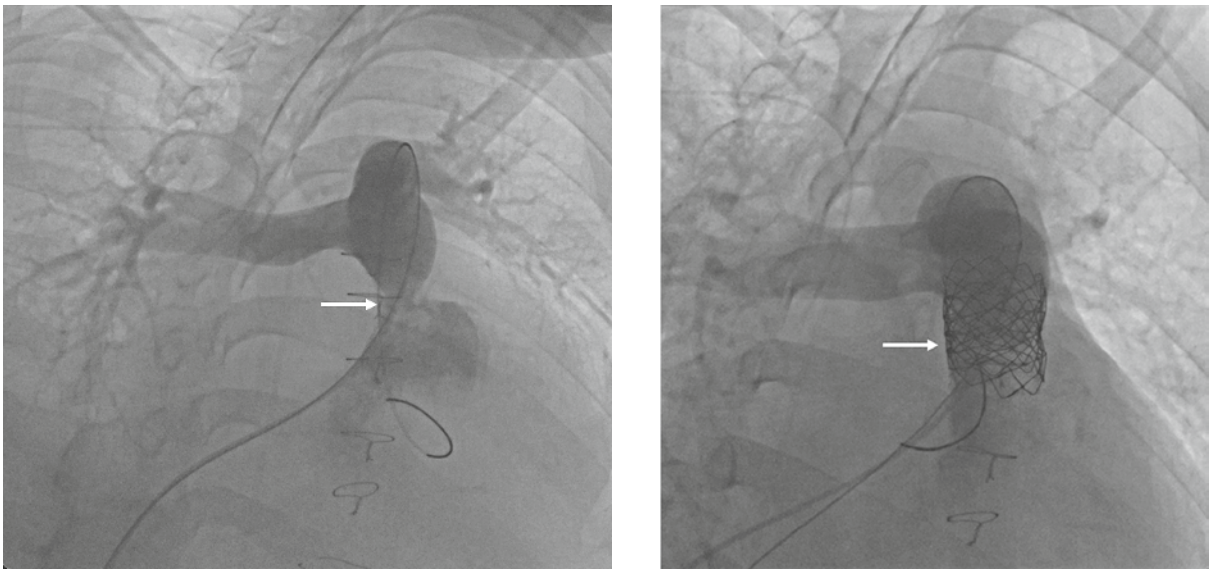
Transcatheter valve replacement

Transcatheter pulmonary valves

The need for reintervention is almost universal among patients with abnormalities of the RVOT and pulmonary valve. Regardless of the prior palliation (whether a RV to PA conduit, transannular patch, balloon valvuloplasty, or replacement of the pulmonary valve altogether), additional interventions can be anticipated over time to address progressive stenosis and/or insufficiency. Conduits, such as those used in truncus arteriosus, pulmonary atresia, some forms of transposition, and the Ross procedure, fail due to stenosis and insufficiency associated with valve degeneration, loss of conduit diameter, and fixed size as the patient grows. The RV consequently becomes pressure and volume overloaded. On the other end of the spectrum are patients with TOF with transannular patches who develop worsening RV dilation due to free pulmonary insufficiency alone. In both cases, RV failure and intractable arrhythmias can result if the stenosis and/or insufficiency are not addressed.

Transcatheter pulmonary valve replacement (TPVR) has revolutionized the management of many of these patients since its introduction two decades ago. Candidates include those who have an adequately sized conduit or native RVOT to accept the available valves [98–100] (Figure 34.15). Broader application is currently limited by the size mismatch between current devices and their landing zones (e.g., a child with a transannular patch may have a dilated RVOT too large to accommodate a TPVR). Devices that are self-expanding and hour-glass in shape have recently become available, however, and may lead to increased utilization in this population [98, 101].

The status of the RV guides anesthetic management and risk assessment. Patients with preserved RV function undergoing TPVR are at low risk for anesthesia-induced hemodynamic instability. Anesthetic techniques can include sedation with attention to increasing depth during stimulating portions (e.g., initial access, sheath upsizing for valve deployment, and ballooning and/or stenting of the existing valve or conduit) or GETA. Lengthy procedural times, the potential for significant procedural complications, and the need to avoid movement during valve deployment bias our management toward the use of GETA. Patients with preexisting RV dysfunction in the setting of long-standing insufficiency or severe conduit or native RVOT stenosis, in contrast, represent



(A) (B)

Figure 34.15 Transcatheter pulmonary valve replacement. A morbidly obese 27-year-old female status post Ross procedure at age 9, now with severe conduit stenosis and severely depressed RV function, presented for TPVR. (A) A severely narrowed and calcified RV-PA conduit is seen (arrow) with regurgitation. (B) After angioplasty, stent placement, and transcatheter pulmonary valve placement (arrow), there is no significant residual stenosis or regurgitation. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.

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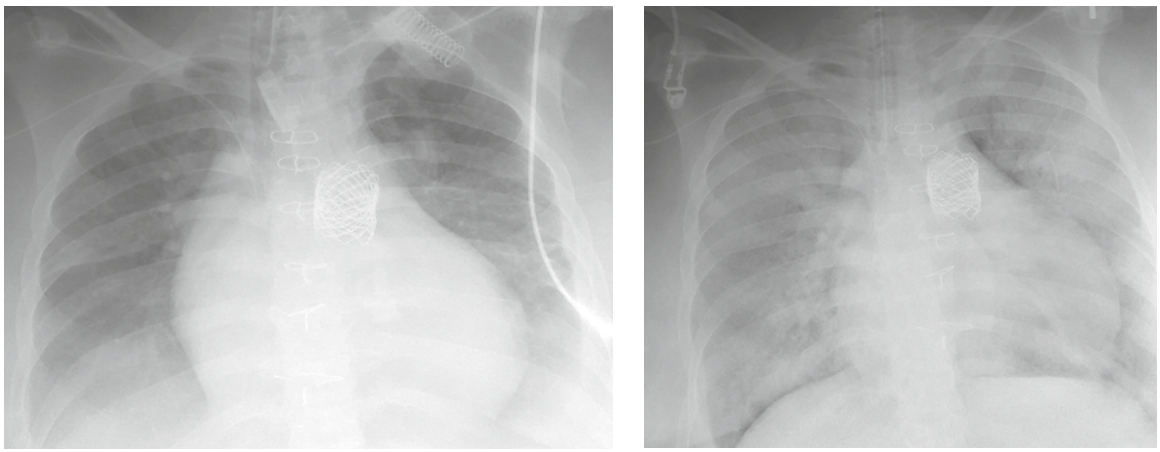
a higher risk group. Such patients may already be receiving inotropic support entering the procedure and may require uptitration and the addition of a vasopressor with the induction of general anesthesia. Occasionally, patients with long-standing RV dilation may also have TR and significant right atrium (RA) dilation, which provides a nidus for atrial dysrhythmias. Maintaining sinus rhythm and age-appropriate systemic blood pressure is central to avoiding RV ischemia in the setting of RV hypertension and elevated RVEDP. Large-bore IV access is routinely obtained to allow for volume resuscitation and vasoactive administration. External defibrillator pads and packed red blood cells need to be immediately available. Additional arterial access apart from that placed by the interventionalist is considered in those with RV dysfunction who may become hypotensive upon induction or with the institution of PPV. Patients who tolerate the procedure well are extubated. Given the large size of the venous sheaths placed (22–24 French), aggressive PONV prophylaxis and analgesia are administered to decrease the risk of bleeding associated with emesis or pain.

Major periprocedural complications include (i) coronary or aortic root compression, (ii) RV to PA conduit rupture, (iii) PA injury, (iv) postdeployment pulmonary edema, and (v) valve malposition/embolization [102–106]. Coronary compression can occur with ballooning of either the RV to PA conduit or the native outflow tract due to proximity of the coronaries to these structures. Consequently, a coronary angiogram is performed simultaneously with RVOT ballooning and after stent and valve placement to ensure coronary patency [100, 105]. Aortic root compression can occur similarly with resulting aortic insufficiency. Partial or total conduit rupture is associated with attempts at ballooning noncompliant conduits, such as those that are heavily calcified and severely stenotic. The subsequent hemorrhage is managed with volume resuscitation and pressor support, while the interventional team places a covered stent to limit further extravasation and a pericardial drain if tamponade develops. Surgery may be needed to provide definitive therapy. PA injury is most common secondary to guidewire perforation and can result in hemoptysis or hemothorax [106]. One lung ventilation may be indicated if severe. Pulmonary edema following the relief of stenosis is thought to be secondary to an acute increase in LVEDP (due to increased PBF) in patients with underlying LV diastolic dysfunction [103] (Figure 34.16). Though this mechanism would suggest a relatively acute presentation, it has also been observed in our institution up to 16 hours after valve deployment. This late presentation may indicate the need for close postprocedural monitoring in the highest risk patients: those with chronic and severe RVOT or conduit obstruction and preexisting LV dysfunction. Management entails aggressive diuresis and supportive mechanical ventilation.

Transcatheter aortic valves

No devices are currently approved for transcatheter aortic valve replacement (TAVR) in the pediatric population. Limitations associated with current devices include their large size (and larger delivery sheaths) relative to that needed for most children. Nonetheless, a transcatheter approach offers a reasonably efficacious alternative to surgery for a select group of children who would otherwise be poor surgical candidates [107].

Underlying LV function and the severity of aortic insufficiency (AI) and/or aortic stenosis (AS) guide anesthetic management. Because this procedure is currently limited to those with a relative contraindication to surgical repair, comorbidities can further guide assessment. GETA is the rule due to the potential for complications, invasiveness, need for TEE, and procedure length. ECMO candidacy or plans otherwise in the event of intraprocedural cardiovascular collapse are determined in advance. As in PDA stenting, the approach to deploy the valve can vary and can impact the location of monitoring lines and pulse oximetry placement. In older patients who have adequately sized femoral vessels, the transfemoral approach is considered. Smaller vessel size

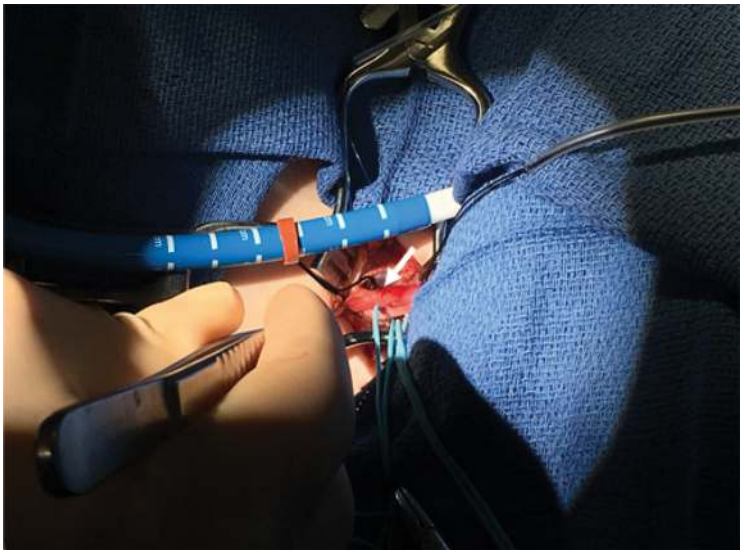


(A) (B)

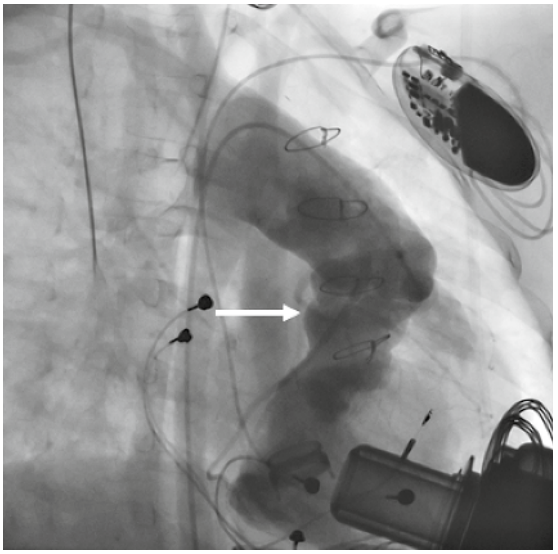
Figure 34.16 Pulmonary edema following transcatheter pulmonary valve replacement. (A) The same patient immediately following transcatheter pulmonary valve replacement. (B) 16 hours postprocedure. The patient developed dyspnea and desaturation requiring re-intubation and ultimately venovenous extracorporeal support. The presumed mechanism was increased preload to a dysfunctional left ventricle resulting in increased left-sided pressures. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

necessitates alternate approaches: a hybrid transapical approach through a thoracotomy and carotid approach via surgical cutdown have been described [107] (Figure 34.17). A dedicated arterial line in addition to the arterial access placed by the interventionalist is obtained, as are large-bore peripheral IVs. Vasoactive agents, blood, external defibrillation pads, and a Foley catheter are indicated. Periods of rapid pacing may be used prior to valvuloplasty and valve deployment. The location of pacing depends on the child's cardiac anatomy but is most often accomplished via the RV. Anticipatory support with boluses of phenylephrine before and after pacing is given.

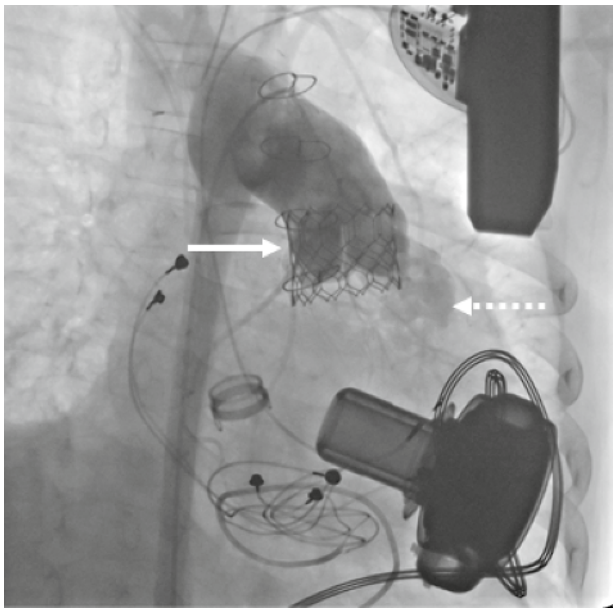
Complications unique to children undergoing TAVR include the higher risk for vascular dissection/disruption due to mismatch between commonly used delivery devices and vessel size. As for transcatheter pulmonary valves, surgical backup should be available (if not already involved for access). Common risks otherwise include those of valve embolization



(A)



(B)



(C)

Figure 34.17 Transcatheter aortic valve replacement via the right common carotid artery. An 8-year-old child status post Heartware® ventricular assist device placement, now with progressive aortic insufficiency. Due to the high risk associated with repeat sternotomy, bypass, and cross-clamping for surgical valve replacement, a hybrid transcatheter approach was selected. (A) The right common carotid artery (arrow) can be seen exposed via a surgical cutdown, chosen for its larger size relative to the femoral artery. Also seen in the picture is the large delivery sheath used for transcatheter aortic valve placement. (B) Significant aortic regurgitation is seen (arrow). (C) A transcatheter aortic can be seen that was placed (arrow), and 3 years later, the transcatheter aortic valve was working well with trivial paravalvar leak (dotted arrow). (Source: Texas Children's Hospital Cardiac Catheterization Laboratory.)

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and coronary compression with valve placement (due to direct obstruction or ostial narrowing with dilation of the annulus) [107].

Hybrid procedures

Hybrid procedures refer to joint surgical and transcatheter interventions occurring in the CCL or operating room. Though most commonly associated with the initial palliation of HLHS, hybrid approaches have also been used in periventricular closure of muscular VSDs, stenting of stenotic pulmonary veins, and valve replacement, among other procedures [108, 109]. The focus of this section is on the hybrid palliation for HLHS.

Basic aspects of this strategy include surgical placement of bilateral pulmonary artery bands (bPAB) via median sternotomy followed by ductal stenting [110] (Figure 34.18). Variations abound, however, as to (i) whether the duct is stented (some centers may choose instead to maintain ductal patency with PGE_1); (ii) when the duct is stented (either during PAB placement or as a separate procedure); (iii) whether or not an atrial septostomy or atrial septal stent is concurrently performed; and (iv) how to address the risk of retrograde aortic arch obstruction (RAAO). Atrial septostomy is often delayed in the absence of an intact/restrictive atrial septum to allow time for the left atrium to grow. With a larger left atrium, a more aggressive ballooning can be performed, leading to a larger and more durable septostomy [111]. RAAO is an important source of morbidity and mortality in HLHS as the coronary and cerebral circulations are reliant on retrograde flow through the transverse arch (entirely so in the variant of aortic atresia). Clinically significant RAAO is present in 10% of HLHS neonates at birth and can occur in an additional 24% following the hybrid procedure [108, 112]. To decrease this risk of myocardial and cerebral ischemia, some centers also perform a reverse Blalock–Taussig shunt (main PA to innominate artery) at the time of ductal stenting in at-risk patients. Others view preexisting RAAO as a contraindication to the hybrid procedure [113, 114]. For patients who develop RAAO subsequent to the hybrid procedure, treatment is achieved with retrograde arch ballooning and stenting.

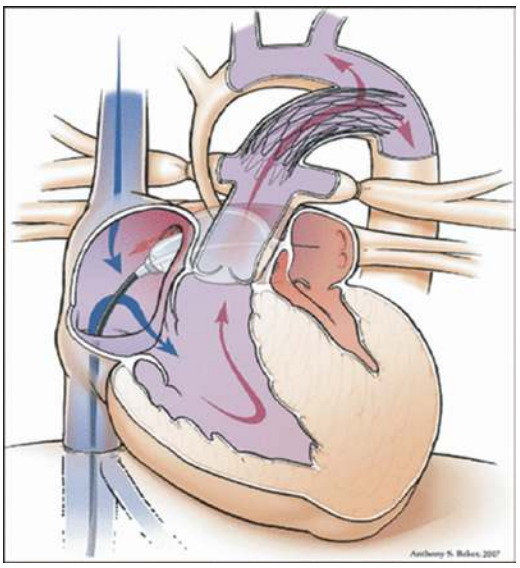


Figure 34.18 Hybrid procedure for hypoplastic left heart syndrome. Common elements include bilateral pulmonary artery bands, transcatheter stenting of the patent ductus arteriosus, and an atrial septostomy or atrial septal stent. (Source: Naguib et al. [110]. Reproduced with permission of John Wiley & Sons.)

The choice of when to use the hybrid approach versus conventional surgical management (the Norwood procedure) is institution specific and often dependent on patient factors. Advantages to hybrid palliation center around its ability to balance $Q_p : Q_s$ without the morbidity associated with cardiopulmonary bypass (and deep hypothermic circulatory arrest or selective cerebral perfusion) in the neonatal period. While few centers use the hybrid approach preferentially, others reserve it for those patients thought to be at highest risk for Norwood palliation. Such patients include those with prematurity, birth weight <2.5 kg, presence of LV to coronary fistulae, intact or restrictive atrial septum, severe RV dysfunction, moderate-to-severe TR, intracerebral hemorrhage, or persistent end-organ injury secondary to shock at initial presentation [115–117]. Disadvantages to the hybrid approach focus on the risk of RAAO, need for repeat catheter interventions prior to stage 2 palliation, impact of the bPAB on PA growth, and the complexity of the comprehensive stage 2 procedure (combined Norwood and bidirectional superior cavopulmonary anastomosis).

Anesthetic concerns specific to the hybrid approach include the potential for instability with bPAB placement and acute RAAO with ductal stent deployment [59, 110]. Arrhythmias, hypotension, and bradycardia may occur with bPAB placement as a result of contact with the left atrial appendage or manual compression of the ductus. Both are more likely to occur with manipulation of the left PA due to its proximity to these structures. Adenosine and cardioversion can be used to treat persistent supraventricular tachycardia (SVT). Compression of the ductus can be particularly threatening due to the transient decrease in myocardial perfusion. Decreases in heart rate and cerebral saturation may be the first signs of ischemia along with ST depression. Epinephrine in bolus doses of 1–10 mcg/kg may be needed to facilitate recovery. Following placement of the bPAB, systemic blood pressure should increase with a coincident decrease in oxygen saturation. If proceeding with ductal stent placement, a sheath is then placed in the main PA and the stent is deployed under fluoroscopic guidance. Because systemic blood flow is transiently altered during stent deployment, instability can also arise during this time. RAAO secondary to stent encroachment into the aorta can manifest as bradycardia, hypotension, and arrest. Monitoring of a right radial arterial pressure and cerebral saturation is recommended to allow prompt detection [59, 110]. Despite these risks, the procedure appears to be well tolerated. Naguib et al. in a review of the anesthetic management of 77 patients undergoing hybrid palliation reported that epinephrine infusions were initiated in only 4 patients and epinephrine boluses were required in only 5. 27% were transfused blood, and 60% of those who were intubated solely for the procedure were extubated at the end of the case. See Chapter 30 for additional discussion of the hybrid approach for HLHS.

Pericardiocentesis

The need for pericardiocentesis may arise acutely during interventional catheterization or more electively in a child with a postsurgical, neoplastic, or infectious effusion. The former may occur during endomyocardial biopsies, interventions at the RVOT (RF perforation in PA/IVS, RVOT stenting, transcatheter PVR, or conduit interventions), or transseptal approaches to the left atrium. Clinically, these acute bleeds can result in precipitous hypotension due to tamponade. Treatment requires emergent pericardial drainage with autotransfusion as indicated [118]. Autotransfusion entails siphoning the blood that is drained (a stopcock can be placed on the drain catheter for pulling blood into a syringe) and immediately returning it to the patient without any delay or storage (see Figure 34.19). Additional nonautologous transfusion is often needed in neonates and infants to maintain intravascular volume. Blood pressure is supported with epinephrine, and protamine may be needed to reverse heparin-induced coagulopathy. Surgery is indicated if the bleeding does not stop with these measures.

Children presenting to the CCL for primary drainage of a pericardial effusion can vary in their clinical presentation. Rarely do they present with signs and symptoms of frank tamponade: low cardiac output as evidenced by anxiety, cool extremities, tachycardia, tachypnea, pulsus paradoxus, and marginal blood pressures [119]. More often, patients appear stable, belying their potential for decompensation. Anesthetic management entails ensuring adequate preload and maintaining SVR, contractility, and heart rate (i.e., fast, full, and tight) [119]. Because stroke volume is relatively fixed in tamponade, marked decreases in heart rate will lead to proportional decreases in cardiac output. Postcardiac surgery patients are often on aggressive diuretic therapy preprocedurally in attempts to decrease the size of their effusions. This population needs volume resuscitation prior to anesthesia.

GETA is avoided to minimize the additional risks of PPV. Spontaneous ventilation is maintained using a combination of ketamine and midazolam. Morphine is not used predrainage because of its potential to decrease SVR, nor are rapid boluses of dexmedetomidine administered due to associated

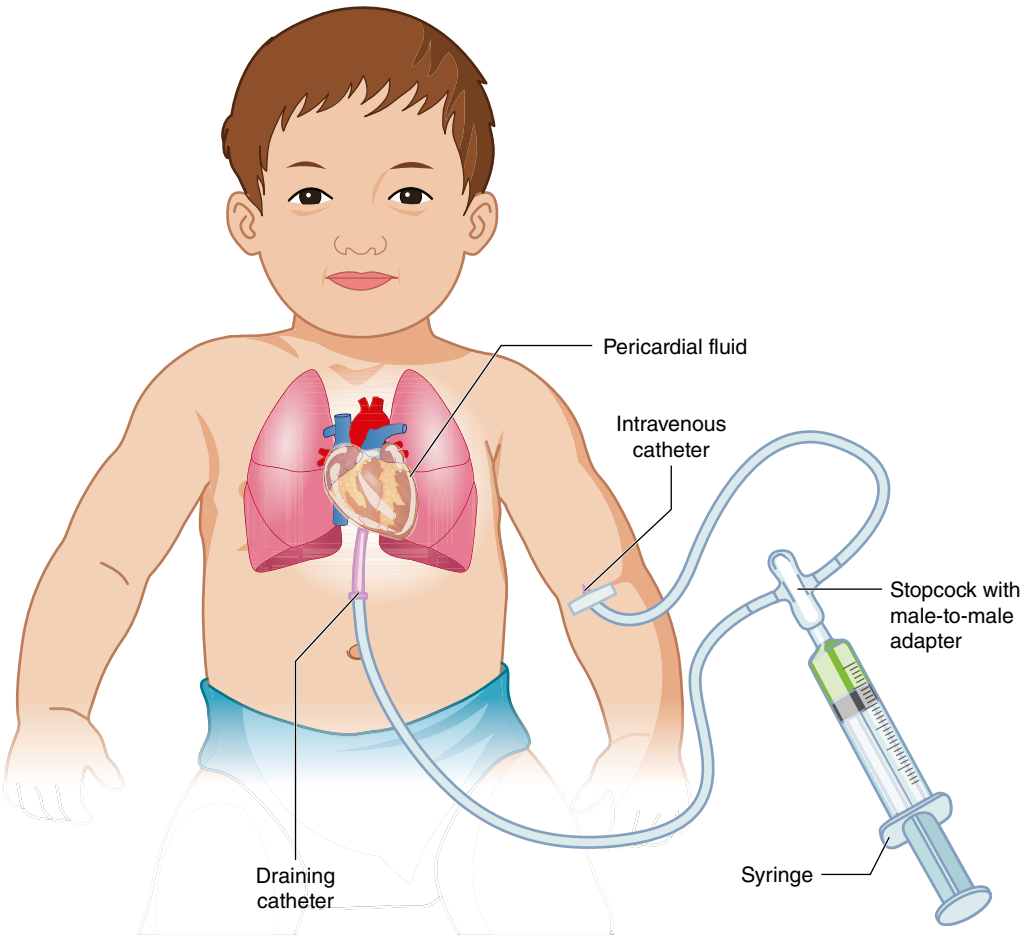


Figure 34.19 Autotransfusion following an acute pericardial bleed. A filter is used prior to reinfusion to avoid embolization of thrombi or fat particles from the pericardial space. Autotransfusion should not be performed when there is suspicion for an infectious or neoplastic effusion to prevent systemic spread. (Source: Mossad [118]. Reproduced with permission of Elsevier.)

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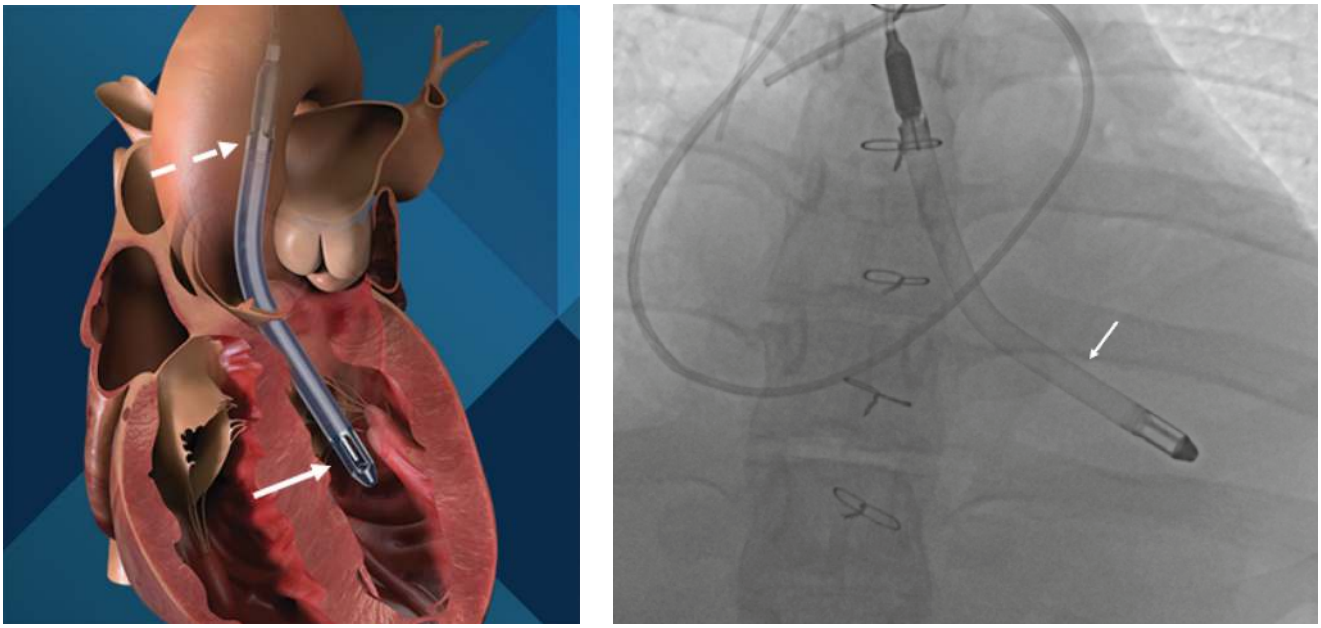
bradycardia. In children in whom the above efforts are ineffective, an alternative strategy is to use low-dose sevoflurane (2–3%) to maintain spontaneous ventilation. Vasopressors and inotropes should be at the ready if needed. Positioning of the patient in the CCL is in the semi-Fowler's position with back elevated at 30°–45° to allow the pericardial fluid to accumulate inferiorly. The airway remains accessible in this position, but if intubation is required subsequently, the patient is positioned supine. The effusion is drained under echocardiographic guidance following local anesthetic administration. Procedural complications include needle- or wire-induced laceration of the ventricle, coronary artery or vein, arrhythmias, or injury to the lungs or esophagus. Postprocedurally, pulmonary edema may develop due to LV dysfunction associated with the acute increase in LV preload [119]. Additional discussion of pericardial effusion is presented in Chapter 31.

Percutaneous mechanical circulatory support

The role of the interventionalist in mechanical circulatory support (MCS) has grown in recent years in parallel with the increased utilization of percutaneous ventricular assist devices (PVADs) in the management of pediatric cardiogenic shock. Such devices may be placed as the primary procedure (e.g., LV decompression while on venoarterial ECMO or as a bridge to a durable VAD, transplant, or recovery) or as a supportive intervention in the setting of another high-risk procedure (e.g., PVAD backup for an endomyocardial biopsy in a patient with presumed acute graft rejection and tenuous hemodynamics).

The oldest of these devices is the intra-aortic balloon pump (IABP). Used primarily in adults, IABPs have also been used in infants and children [120–124]. IABPs assist the failing ventricle by augmenting diastolic perfusion pressure and decreasing afterload by timing balloon inflation to diastole and deflation to systole [124]. Constraining its use in pediatrics has been the limited support it offers in florid ventricular failure, and technical challenges in timing balloon inflation and deflation to changes in rate and rhythm. Nonetheless, as volumes of adults with CHD increase in pediatric centers, this therapy may experience a resurgence.

A more recent introduction has been the off-label use of the Impella® Heart Pump (Abiomed Inc., Danvers, MA) [125, 126]. The Impella is a continuous axial flow device that extracts blood from the failing ventricle and delivers it to the aorta (Figure 34.20). In doing so, it unloads the ventricle and augments cardiac output. Available configurations include the Impella 2.5, cardiac power (CP), 5, and 5.5, which, respectively, provide flow rates of up to 2.5, 4.3, 5, and 6.2 L/min (Table 34.7). The specific device used is guided by patient size and the indication for support. Most commonly, the 2.5 and CP are used for younger patients or those on ECMO in need of LV decompression. The 5 and 5.5 are used for larger patients and those in need of the higher flows that these devices can provide. The device used, procedural urgency, and anticipated duration of support inform placement at either the femoral artery or surgical cutdown at the axillary artery. Fluoroscopy



(A) (B)

Figure 34.20 Left ventricular support with the Impella 5.5. (A) Blood is entrained through the device inlet located in the left ventricle (arrow) and ejected into the ascending aorta through the blood outlet (dotted arrow). (B) Impella placement (arrow) via a left subclavian cutdown approach in a 17-year-old status post heart transplantation with acute rejection. A pulmonary artery catheter is also seen and used for postprocedural management. (Sources: Image A from https://www.heartrecovery.com/products-and-services/impella/impella-55-with-smartassist. Image B from Texas Children's Hospital Cardiac Catheterization Laboratories.)

Table 34.7 Characteristics of and indications for the different Impella heart pumps

	Insertion site	Indications	Maximum flow (L/min)	Pump motor/catheter diameter (Fr)
2.5	Percutaneous femoral or axillary arteries	• VA ECMO LV unloading	2.5	12/9r
CP	Percutaneous femoral or axillary arteries	• VA ECMO LV unloading • Temporary LV support	4.3	14/9
5.0	Percutaneous femoral or via surgical graft onto the axillary artery	• Temporary LV support • Bridge to VAD or OHT	5.0	21/9
5.5	Percutaneous femoral or via surgical graft onto the axillary artery	• Temporary LV support • Bridge to VAD or OHT	6.2	19/9
RP	Femoral venous only	• RV support	4.6	22/11

ECMO, indicates extracorporeal membrane oxygenation; LV, left ventricle; OHT, orthotopic heart transplant; RV, right ventricle; VA, venoarterial; VAD, ventricular assist device.

and TEE guide placement. Echocardiographic features predicting successful placement include a minimum LV apex to aortic valve length of 7.5 cm and an aortic annulus >1.5 cm, corresponding with an average weight of 23 kg and body surface area (BSA) of 0.89 m^2 [127]. (Morray 2019). The youngest patient to date supported with an Impella was a 4-year-old weighing 15 kg with a BSA of 0.67 m^2. RV support can also be provided by the Impella RP, which has been used in a child as young 14 years of age with a BSA of 1.4 m^2 [126].

Although sedation has been used for femoral Impella placement, our usual strategy in patients not already intubated is to proceed with GETA. The usual considerations for high-risk patients apply and include the availability of blood, vasoactive agents, adequate venous and dedicated arterial access, defibrillation pads, and the preprocedural determination of ECMO candidacy in the event of arrest. A surgical cutdown at the axillary artery with placement of a chimney graft adds to the duration of the procedure both due to the dissection and the time needed to pass the device through the graft. If the arterial line used for monitoring is on the same extremity as that used for axillary device placement, a brief period of dampening is to be expected. Arrhythmias during placement are common due to ventricular ectopy. TEE guidance is essential to diagnose complications such as deep placement within the LV that may entangle the mitral valve chordal apparatus, or incomplete coaptation of the aortic valve leaflets causing new insufficiency [128]. The Impella monitoring screen can help in assessing device placement once TEE is removed [129] (Figure 34.21). Once proper positioning is confirmed, the Impella is initiated between P0 and P9: the higher the number, the greater the revolutions per minute and therefore flow support. Anticipated hemodynamic changes include an overall increase in cardiac output with a decrease in native stroke volume and pulmonary capillary wedge pressure. Vasoactive support is usually not changed in this acute period as the RV may still need support to provide LV filling. Prior to returning to the ICU, a Swan-Ganz catheter is commonly placed to guide ICU management for escalating or weaning support. Periprocedural complications include limb ischemia, vascular injury, bleeding, hemolysis, suction events, and device failure [125]. Anticoagulation is maintained with heparin through the device's purge fluid, and if inadequate, systemic heparin is added.

The use of ECMO in the CCL, still the most common type of MCS in children, warrants further discussion. For high-risk patients who may require ECMO during the procedure, consideration should be given to scheduling the procedure in the lab that is most suited to ECMO. Such a lab is usually large, with adequate oxygen and air attachments to accommodate both the ECMO circuit and anesthesia machine. Moreover, the ECMO circuit should be easily positioned within the room, with unimpeded entry into and exit from the lab. Similar considerations apply for patients already on ECMO who need a diagnostic or interventional procedure. Extensive further discussion of MCS is presented in Chapter 37.

KEY POINTS: INTERVENTIONAL CATHETERIZATION

- The range of interventions possible continues to expand with recent growth in the areas of ductal stenting, pulmonary vein intervention, TPVR, MCS, and transcatheter closure of PDAs in premature infants.
- A corollary of this growth is an increase in the acuity and complexity of the patients presenting to the CCL.
- Such complexity underscores the need for anesthesia involvement in the planning of these increasingly high-risk procedures and for awareness of the unique complications that can arise and how to manage them.

Adverse events

Adverse events associated with catheterization can be related to the procedure, anesthetic, or environment of the catheterization suite [46, 130–132] (see Table 34.8). While the majority of such events are well tolerated and resolve with either minimal or no intervention (e.g., transient catheter-induced arrhythmias or superficial hematomas at vascular access

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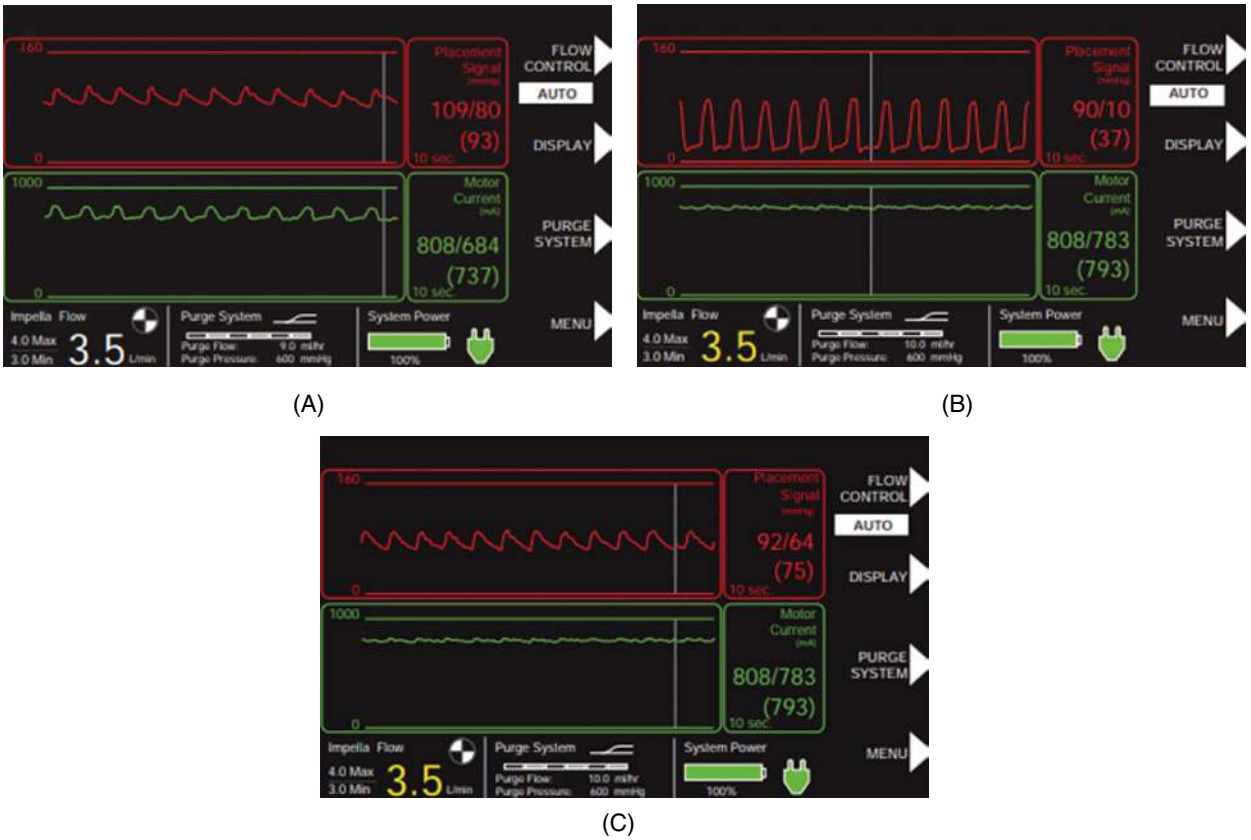


Figure 34.21 Impella controller screen can indicate device malposition. The Impella device can move either into or out of the left ventricle with patient movement. Depicted here are images of the controller screen in the Impella 2.5 and CP. Other models have similar appearances. (A) Correct positioning with both an aortic pressure tracing and pulsatile motor current. (B) Displacement of the device into the left ventricle indicated by a ventricular pressure tracing and flat motor current. (C) Displacement of the device into aorta with an aortic pressure tracing and flat motor current.

Table 34.8 Adverse events during cardiac catheterization

Vascular injury	1.11 (%)	Neurologic injury	0.13
• Access site complications	0.87	• Stroke (air/thrombus)	0.08
• Arterial thrombosis/occlusion requiring treatment	0.67	• Seizure	0.04
• Venous thrombosis/occlusion requiring treatment	0.06	• Brachial plexus injury	0.01
• Other vascular injury	0.40		
• Rebleeding require transfusion	0.09	Airway complications	
• Retroperitoneal hematoma	0.03	• Accidental extubation during procedure	0.02
• Cardiac perforation	0.15	• Extended need for mechanical ventilation	0.04
• Pericardial effusion requiring drainage	0.09	• Conversion from natural to artificial airway	1.77[b]
Hemodynamic instability	1.19	Desaturation	
• Unstable arrhythmias	0.32	• Respiratory: pulmonary edema/hemoptysis	
• Complete heart block requiring pacing	0.14	• Circulatory: increased shunting/PVR	
• Instability requiring inotropy and/or compressions	0.87	• Mechanical: TEE/TTE probe, pneumothorax, obesity	
• Unplanned ECMO	0.12	Contrast toxicity	
		Hypothermia	
New or significantly worsened valvular regurgitation	0.07–0.09[a]	Endocarditis	0.02
Unanticipated transfusion	0.51	Cardiac arrest	0.18–0.96%[c]
Device migration or embolization	0.44		
Balloon rupture with vascular damage/device complication	0.24		

Source: Modified from references [46, 132–134].

[a] Hill et al. [132] and Jayaram et al. [133].

[b] Lin et al. [134].

[c] Odegard et al. [46].

sites), significant life-threatening events can and do occur. Termed major adverse events (MAEs) or serious adverse events (SAEs) depending on the reporting registry, these complications can cause mortality or permanent morbidity and are characterized by an escalation in support, further catheter-based or surgical intervention, and/or an extended length of stay. Examples include pulmonary hemorrhage resulting in hypoxemia and chest compressions, or catheter-induced third- degree heart block requiring transvenous pacing.

MAEs occur in 2–7% of all congenital cardiac catheterizations [130, 131, 133–135]. The wide range is attributable to the varying definitions of what constitutes such events. The most common causes reported include access site complications, hemodynamic compromise requiring inotropic support and/or chest compressions, unanticipated blood transfusion, and hemodynamically unstable arrhythmias requiring electrical and/or pharmacologic therapy. For the subgroup of interventional procedures, the leading causes of high severity events are device or stent migration, malposition, or embolization.

Mortality related to catheterization is rare and ranges between 0.08 and 0.29% [130–132]. Cardiac arrest occurs with a higher frequency, with one group reporting 0.7% [128] and another 0.96% [46]. As a reference, the benchmark estimate of the incidence of perioperative cardiac arrest in all pediatric patients is 0.014% [136].

Significant complications associated with anesthetic induction and airway management appear to be infrequent. In one series of 29,830 pediatric patients from 27 centers, cardiac arrest with induction of anesthesia was observed in 0.12% of all procedures [130]. Airway complications, including accidental extubation during the procedure, failed extubation, unanticipated need for intubation during/after the procedure, and postextubation stridor or laryngospasm, occurred in 0.16% [130]. In another review of 13,611 pediatric patients at eight centers, the most common reported anesthesia- and sedation-related adverse event was hypotension [132]. This occurred in 93 (0.68%) patients and was observed primarily with anesthetic induction. While the majority of hypotensive events were minor-to-moderate in severity, some were associated with cardiopulmonary resuscitation (CPR) and ECMO. High severity events associated with anesthesia, sedation, and airway management were observed in 94 (0.69%) patients, with an overall mortality within this group of 0.015% [132].

Risk assessment

Several risk scoring and risk adjustment models have been developed to identify key contributors to significant adverse events [130, 131, 134, 135, 137, 138]. A consistent theme among these models is the influence of procedural complexity and patient characteristics in determining risk.

Because there are over 200 interventional procedures that may be performed, procedural risk categories were developed to group together those procedures with similar risk [131] (Table 34.9). These categories were based on expert consensus and empirical data. The impact of procedure type on the risk of an MAE can be observed by their associated odds ratios (ORs). A category 2 procedure carries an OR of an MAE of 1.79, whereas a category 6 procedure carries an OR of 9.69. Odegard et al. reported the highest incidence of cardiac arrests in patients undergoing VSD closure (11.9/100 procedures), intervention for intact atrial septum in patients with an atrial restriction (10.0/100 procedures), and pulmonary vein angioplasty (3.6/100 procedures) [46]. These are all defined as category 5 procedures. Of note, diagnostic catheterizations are generally lower risk than interventional ones. An important exception is diagnostic catheterization in neonates and infants.

Patient characteristics are equally significant (Table 34.10). Of patient-specific variables, age <1 year, weight <5 kg, single-ventricle physiology, chromosomal abnormalities, genetic syndromes, and noncardiac comorbidities all increase risk [131]. Among the subgroup of patients aged <1 year, neonates and those weighing <2.5 kg are most likely to experience adverse events. That patients with single-ventricle physiology are at increased risk is consistent with data reported in the Pediatric Perioperative Cardiac Arrest Registry [139]. Within this group, ductal- or shunt-dependent lesions and failing Glenn or Fontan physiologies are most concerning. Examples of other high-risk diagnoses include patients with cardiomyopathies with depressed systolic function, LV outflow tract obstruction (specifically unrepaired supravalvar AS), and PH [130]. Of the latter group, patients with suprasystemic pulmonary pressures, premature neonates, and non-premature infants are at increased risk of catastrophic adverse events [22, 28]. A final population warranting mention are heart transplants with CAV or acute rejection [22]. Such patients are predisposed to myocardial ischemia, ventricular dysrhythmias, and cardiac arrest at baseline.

Of the noncardiac comorbidities observed in patients presenting for catheterization, chronic lung disease is most common. The highest ORs for complications, however, are associated with renal insufficiency, hepatic disease, and coagulation abnormalities [131]. These findings may occur independently of the underlying cardiac disease or represent sequelae of poor cardiac output.

Preprocedural status can further inform a patient's risk. A child requiring vasoactive infusions (including PGE_1) or antiarrhythmics prior to catheterization begins with a lesser margin to tolerate anesthetic- or catheter-induced instability. Precatheterization hemodynamic variables such as systemic or mixed venous desaturation, or evidence of elevations in PVR, $Q_p : Q_s$, or systemic ventricular EDP are also factors associated with complications [130, 131, 135]. While some of these data can only be quantified during the catheterization itself, one can qualitatively assess many of these physiologic variables preprocedure based on prior history, clinical evaluation, and echocardiography.

When examining risk factors in *adults* with CHD undergoing catheterization, many of the same contributors are observed: procedure type, comorbidities, and certain physiologic variables [134, 140, 141]. In one model reviewing data from 87 hospitals in the United States, the strongest variables predicting MAEs were procedure complexity and urgency. Other factors of importance included a history of renal disease, preprocedural anticoagulant use, lower hemoglobin, and older age (Figure 34.22). The physiologic factors indicating risk included a lower oxygen saturation, pulmonary hypertension, elevated systemic ventricle EDP (≥18 mmHg), and a cardiac index less than 2.8 L/min/m^2 [134, 141].

In both pediatric and adult populations, institutional case volume appears to impact the MAE rate. Complications

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Table 34.9 Procedure-type risk categories

	Risk category 1	Risk category 2	Risk category 3	Risk category 4	Risk category 5	Risk category 6
Odds ratio for MAEs	Reference	1.79	3.69	3.63	7.18	9.69
Diagnostic		Diagnostic cath (age > 1 yr)		Diagnostic cath (age 30 d to 1 yr)		Diagnostic cath (age < 30 d)
Valvuloplasty		Pulmonic valvuloplasty (age > 30 d)		Aortic valvuloplasty (age > 30 d)	Aortic valvuloplasty (age < 30 d) Pulmonic valvuloplasty (age < 30 d)	
Device or coil closure		ASD/PFO Coronary artery fistula PDA (weight > 6 kg) Fontan fenestration or baffle leak	Systemic artery (excluding aorta) or systemic vein Pulmonary or systemic AVM Perivalvular leak	PDA closure (weight 3–6 kg) Systemic artery to PA connection Systemic vein to PV connection	VSD PDA (weight < 3 kg)	
Balloon angioplasty		Conduit	Angioplasty for CoA Proximal or distal PA Fontan baffle/ fenestration	Caval or noncaval vein Atrial septum s/p atrial switch	Atrial septum Dilation of sano Systemic artery (other than aorta) Systemic to PA shunt	
Stent placement		Conduit	Stent placement for CoA Proximal or distal PA Fontan baffle/ fenestration	Caval or noncaval vein Atrial septum s/p atrial switch	Atrial septum Dilation of Sano Systemic artery (other than aorta) Systemic to PA shunt	
Stent redilation		Stent redilation (other than for CoA)	Stent redilation for CoA			
Other	Myocardial biopsy s/p OHT	Elective pericardiocentesis	TPVR Myocardial biopsy (excluding OHT)	Snare foreign body Balloon valvotomy of mitral valve	BAS Perforation of atretic pulmonary valve Atrial septal perforation	

Source: Reproduced with permission from Jayaram et al. [131].
ASD, indicates atrial septal defect; AVM, arteriovenous malformation; BAS, balloon atrial septostomy; CoA, coarctation of the aorta; MAE, major adverse event; OHT, orthotopic heart transplantation; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TPVR, transcatheter pulmonary valve replacement; and VSD, ventricular septal defect.

were highest in those centers performing fewer than 150 cases annually, and conversely, catastrophic complications were observed least in centers with the highest volumes [131, 142].

The question of whether or not general anesthesia with an airway device represents a higher risk for MAEs compared to sedation with a natural airway is unclear. Lin et al. compared outcomes in these groups and found that even when adjusting for procedural risk, hemodynamic factors, and age, an artificial airway was an independent predictor of MAEs and also had a higher OR for adverse events compared to a natural airway [132]. The authors suggested caution in interpreting these results, however, given the potential for unmeasured characteristics or other confounders. Risk for conversion from natural airway to intubation, observed in 1.8% of the patients reviewed, was associated with younger patients (infants), need for inotropic support, and high-risk procedures. A primary conclusion was that while sedation with a natural airway is safe and effective in low-risk patients and procedures, high-risk patients undergoing high-risk procedures are at risk of MAEs regardless of the airway management strategy. The type of anesthesia used in adults (sedation with natural airway vs. GETA) has not been found to predictive of MAEs [134].

KEY POINTS: ADVERSE EVENTS AND RISK ASSESSMENT

- MAEs associated with catheterization are infrequent, but the highest proportion are composed of access site complications, dysrhythmias, unanticipated transfusion, and device migration.
- Key variables that predict risk include the specific procedure and patient characteristics such as age, weight, cardiac diagnosis, comorbidities, and preprocedural physiologic status.
- The need for conversion from a natural airway to an artificial one is associated with age < 1 year, need for inotropy during the catheterization, and high-risk procedures.

Table 34.10 Patient factors associated with increased risk

Age	<1 year (highest in <30 days)
Weight	<5 kg (highest in <2.5 kg)
Chromosomal abnormalities	Trisomy 18
	Trisomy 21
	22q11
Genetic syndromes	Williams-Beuren
	Alagille syndrome
	Heterotaxy
SV physiology	HLHS with restrictive or intact atrial septum
	Ductal or shunt dependent
	Failing Glenn or Fontan circulations
Diagnoses otherwise	OHT with CAV or rejection
	Aortic or mitral stenosis
	Cardiomyopathy with depressed function or obstruction (HCM)
	Systemic-to-suprasystemic PAP (severe PH)
	PA/IVS with RV-DCC
Preprocedural physiologic status	On PGE_1, antiarrhythmics, or MCS
	Systemic desaturation (highest with <65%)
	Dynamic subpulmonary obstruction
	Hypercyanotic spells
	Severe systemic AVVR
	RVSP suprasystemic
Noncardiac comorbidities	Renal insufficiency
	Hepatic disease
	Coagulation abnormalities
	Chronic lung disease

AVVR, atrioventricular valve regurgitation; CAV, coronary allograft vasculopathy; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; OHT, orthotopic heart transplant; MCS, mechanical circulatory support; PA/IVS, pulmonary atresia/intact ventricular septum; PAP, pulmonary artery pressure; PGE_1, prostaglandin E_1; PH, pulmonary hypertension; RV-DCC, right ventricle-dependent coronary circulation

Anesthetic management

Operator-directed sedation versus anesthesia care

The past two decades have seen a transition toward the use of anesthesiology care in place of operator-directed sedation (ODS) for the majority of catheter-based procedures worldwide. As of 2018, ODS was used in only 3% of cases reported to the IMPACT (IMproving Pediatric and Adult Congenital Treatments) registry, down from 19% in 2011 [143]. Several factors have driven this change, but foremost among them has been the shift in procedure type from diagnostic to interventional catheterization, with the latter associated with longer procedure times, complexity, and risk [144]. The benefit of increased anesthesia involvement has been previously demonstrated with a reduction in the frequency of cardiac arrests at one institution [46].

Nevertheless, given the spectrum of providers who can be involved in sedating and monitoring patients in the congenital cardiac catheterization lab, consensus guidelines were developed in 2016 to provide guidance on which cases should involve which providers [145]. Based on an assessment of risk as determined by the Catheterization Risk Score for Pediatrics (CRISP), it was suggested that patients with a higher CRISP score (and therefore higher risk) should be delegated to either an anesthesiologist with expertise in CHD or a pediatric cardiac anesthesiologist, whereas those with lower CRISP scores could be managed by ODS or a sedation team. A recent comparison between the adverse event rates in cases using ODS versus general anesthesia, however, revealed that this approach to provider selection may not be applicable to all settings [143, 144]. Both in observed results and when adjusted for case risk, fewer MAEs were observed with ODS than with general anesthesia. While this association did not persist when assessing only patients aged <18 years, this study nonetheless demonstrated that ODS may be safely administered to a broader range of patient risk categories than previously believed.

Variable	Points
Age 19–40	1
Age 41–65	2
Age >65	3
Underweight body-mass index (adjusted for age)	2
Pre-procedural oxygen saturation <96%	2
No history of prior cardiac catheterizations or surgeries	2
Pre-procedural anticoagulation	3
History of renal insufficiency	3
Hemoglobin <6.8 mmol/L	4
Moderate risk procedure	5
High risk procedure	5
Urgent procedure	7
Emergency/salvage procedure	15

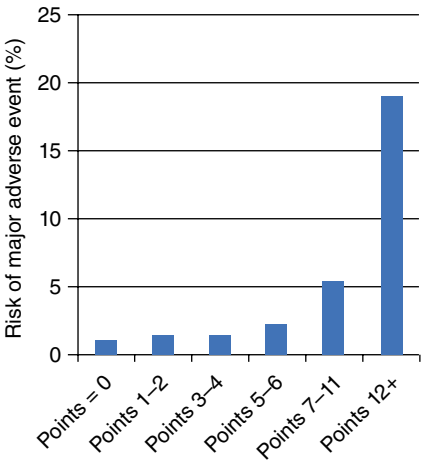


Figure 34.22 Predictors of major adverse events associated with catheterization in adolescents and adults with congenital heart disease. (Source: Reproduced with permission from Schmidt et al. [140])

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Implicit in these findings is that the institution providing ODS is experienced in choosing patients appropriate for sedation versus general anesthesia and is properly structured in both training sedation personnel and developing pathways should an escalation of care be needed. Whether or not these findings are generalizable to resource-poor settings or to those institutions considering the initiation of an ODS program remains unclear. Prospective studies comparing ODS and general anesthesia, and specifically evaluating the effects of sedation regimen and patient and procedural risk factors, are needed [144, 146].

Periprocedural planning

Risk mitigation begins prior to the patient's entry into the CCL, and for outpatients, even prior to hospital arrival. This entails coordination with the catheterization team regarding preprocedural screening, medication management, and even case order such that *nil per os* (NPO) times are minimized in at-risk patients.

A primary goal of preprocedural screening is to identify any recent changes in health that may adversely affect the periprocedural course. The presence of an ongoing or recent respiratory tract infection within 2 weeks of the planned procedure is a common finding that confers an increased risk of perioperative respiratory adverse events [147, 148]. Beyond the immediate negative consequences of laryngospasm, bronchospasm, and persistent desaturation, these complications may also render hemodynamic measurements unreliable and, therefore, affect clinical decision-making. Whether or not to reschedule such patients can be made based on the indication and urgency of the catheterization as well as the severity of symptoms. Our approach is a conservative one in which patients with recent or ongoing respiratory infections are commonly rescheduled to a minimum of 2 weeks following the resolution of symptoms.

A review of the patient's medications can also provide insight into the potential for medication-related complications. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) have been associated with hypotension when taken in proximity to the induction of general anesthesia. Anecdotally, these effects can be particularly pronounced during catheterization due to the relative lack of stimulation compared to surgery. We consequently ask that these medications be held for 24 hours prior to catheterization. Further, diuretics like furosemide are held the morning of the procedure with the understanding that an IV dose may be needed subsequently. The management of antiplatelet agents and anticoagulants like warfarin or the non-vitamin K oral anticoagulants (NOACs) should be discussed on a case-by-case basis [149, 150] (Figure 34.23). The planned procedure, relative risk of bleeding versus thrombosis with continuing versus holding therapy, and the availability of reversal agents particularly for the NOACs can inform this discussion. Other cardiac medications like beta-blockers, antiarrhythmics, and pulmonary vasodilators used for the treatment of PH are commonly continued on the day of the procedure.

For procedures on neonates, infants, or patients otherwise at risk for complications from hypovolemia or hypoglycemia, consideration should be given to a morning rather than afternoon start time. Given the occasionally unpredictable length of interventional catheterizations, communication with pre-cath nursing is essential to ensure that the fasting period is not unnecessarily prolonged for patients scheduled as the second or third cases. We provide clear liquids up to an hour prior to the procedure and, in select cases, initiate IV access to maintain hydration.

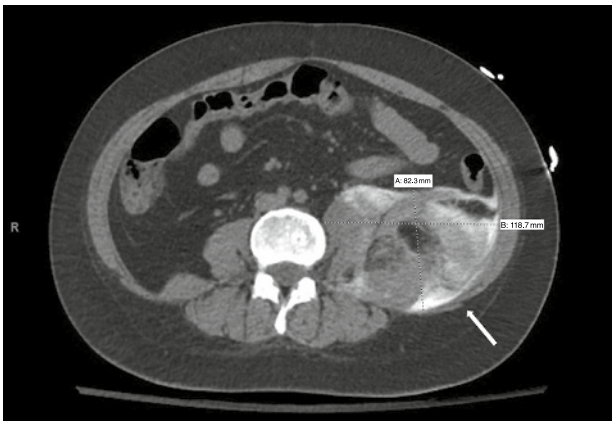


Figure 34.23 Retroperitoneal hematoma demonstrated by computed tomography scan following arterial injury associated with femoral arterial access (arrow). The severity of the bleeding in this patient was related to preprocedural continuation of apixaban, a non-vitamin K antagonist oral anticoagulant. Treatment entailed administration of prothrombin complex concentrate and tranexamic acid. (Source: Texas Children's Hospital Department of Radiology.)

Other key preprocedural factors to consider include the availability of packed red blood cells, postprocedure disposition, and support for high-risk patients. Based on patient weight, comorbidities, and the procedure's risk for bleeding, one can develop a strategy for blood ordering. To promote consistency among our providers and improve the availability of type-specific blood when needed, Texas Children's Hospital Heart Center adopted the following approach noted in Table 34.11. Postprocedural disposition is based on the patient's procedure, comorbidities, and intraprocedural course. During the preprocedure timeout, we tentatively assign status to home discharge versus admission to the inpatient ward or ICU, and once again reevaluate disposition at the procedure's conclusion. Lastly, support for high-risk patients can entail a wide range of equipment needs and multidisciplinary coordination that underscore the importance of early recognition, planning, and communication [59]. For the anesthesia team, preparation often includes the setup of additional invasive monitoring lines, vasoactive support, inhaled pulmonary vasodilators, and/or defibrillation pads depending on both patient and procedural risk factors. For the cardiology team, ancillary equipment like transesophageal echocardiography, percutaneous ventricular support devices, or pacing catheters may be indicated. Certain patients may also prompt consideration for ECMO for either standby or elective initiation. Indications for the former include high-risk anesthetic inductions or concerns for significant procedural instability. Elective initiation of ECMO, on the other hand, is often pursued to allow a procedure to be performed in an otherwise unstable patient. Both forms of

Table 34.11 Approach to facilitate blood ordering and availability for catheterization procedures

Blood ordered *and* in the room	• <5 kg, regardless of the procedure
	• If >5 kg AND undergoing an intervention that is moderate-to-high risk for bleeding, including but not limited to
	  ○ Angioplasty/stenting of an intracardiac- or extracardiac structure
	  ○ Percutaneous valve replacement
	  ○ Pericardiocentesis
	  ○ VSD device closure
	  ○ Transhepatic or transsplenic access
	  ○ Recanalization procedure
	  ○ BAS

Type and screen only	• If cyanotic and undergoing a diagnostic-only evaluation • All inpatients have a type and screen at minimum

No type and screen	• Procedures at low risk for bleeding
	  ○ PDA device closure in the non-premature population
	  ○ ASD device closure
	  ○ Endomyocardial biopsies

ASD, atrial septal defect; BAS, balloon atrial septostomy; PDA, patent ductus arteriosus

ECMO require advance planning with surgery and the ECMO specialists. To ensure that all potential aspects of preprocedural care are anticipated, a checklist tailored to institutional practice that highlights many of the above concerns can be helpful (Table 34.12) [145, 151].

Anesthetic techniques

A variety of anesthetic approaches have been described in patients undergoing catheterization, including spinal or caudal epidural anesthesia, general anesthesia with or without an artificial airway, and sedation with a natural airway. As can be inferred by this breadth of management, no specific anesthetic technique can be recommended for all patients. Rather, anesthetic strategy should be guided by patient and procedural risk factors and an understanding of the pros and cons of the planned technique on both the individual patient and the goals of the proposed procedure.

Advantages of sedation with a natural airway include the potential for greater hemodynamic stability and a more preserved cardiac output in comparison to general anesthesia with PPV. PPV decreases venous return to the heart, thereby decreasing cardiac output and flows across valves and shunts. General anesthesia may also be associated with a more pronounced decrease in SVR and myocardial contractility while also further reducing oxygen consumption [5, 152]. Consequently, the data yielded with general anesthesia and PPV may less accurately reflect the patient's baseline physiology than sedation with spontaneous ventilation. Sedation, however, can be a difficult to control continuum ranging from anxiolysis to conscious sedation to general anesthesia without an airway. As such, the potential benefits of sedation must be weighed against the risks of over-sedation (hypoventilation, airway obstruction, apnea, escalation in airway support, hypotension, and aspiration) and under-sedation (awareness, pain, and movement during inopportune times). Each of these events would negatively affect the quality of data obtained in addition to increasing patient risk. Of note, among patients initially managed with a natural airway, Lin et al. reported that the risk of converting to intubation

Table 34.12 Periprocedural checklist to optimize planning and coordination

Preprocedure	Intraprocedure	Postprocedure
• Confirmation of patient, diagnosis, interventionalist, and procedure • Documented H&P and signed consents • Documentation of allergies (including contrast) • Verified NPO status • Pregnancy test if indicated • Airway status and availability of specialized equipment if difficulty anticipated • Bleeding risk assessed and blood ordered if needed • Availability of implanted devices • Room setup including iNO, TEE, and rotational angiography • Access plan (any known vascular occlusions?) • Anesthesia plan (GA vs. MAC) • Postprocedural disposition (is a bed available if ICU planned?) • Availability of special medications: e.g., vasoactive agents, antiarrhythmics, antibiotics, anticoagulants, or stress-dose steroids • Consideration of the need for ECMO support and surgical backup	• Patient again identified with diagnosis and procedure • Allergies reviewed • Antibiotic needs discussed • Heparin plan • Plan for contrast • Patient position confirmed • Anesthesia plan and use of room air confirmed • Blood availability confirmed if needed • Planned implants available • Specialized equipment/personnel available • Planned disposition reviewed	• All specimens identified, labeled, and sent • Safeguard dressing (time placed, amount of air) if used • Disposition • Need for postprocedural testing or medications • Blood returned if no longer needed • Adverse events • Equipment issues • Review areas for improvement

Source: Modified from Odegard et al. [145].

ECMO, extracorporeal membrane oxygenation; GA, general anesthesia; H&P, history and physical examination; iNO, inhaled nitric oxide; MAC, monitored anesthesia care; NPO, *nil per os*; TEE, transesophageal echocardiography

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was highest in younger patients (specifically infants), those undergoing high-risk procedures, and those needing inotropes or pressors [132]. Sedation with a natural airway, then, may be most safely administered in a child, adolescent, or adult with compensated heart disease undergoing diagnostic catheterization or an otherwise low-risk interventional procedure. Given the potential to escalate airway management in all patients undergoing sedation, accessibility of the airway should also be considered. Extensive draping for neck access and the arms up position can hinder access to the airway relative to procedures involving only groin access. These limitations can be overcome by strategic draping and communication with the cardiologist.

Counterintuitively, sedation may offer the best approach in certain categories of even the sickest patients (e.g., an older child or adolescent status post heart transplant being evaluated for rejection, or a comparably aged patient with a failing Fontan circulation undergoing hemodynamic evaluation). For these and other select classes of patients and procedures, the risks of GETA may exceed the risks of sedation. Assuming adequate patient preparation, reassurance, and cooperation, diagnostic catheterizations in such patients can often be achieved with a combination of IV sedation and generous local anesthetic infiltration. Communication between the cardiologist and the anesthesiologist is particularly important in these cases to allow anticipation and treatment of painful portions of the procedure (i.e., initial infiltration of local anesthetic, placement of sheaths, and later sheath exchanges and removal). As always, one should be prepared to escalate care as indicated.

GETA, on the other hand, may be most suitable for neonates, infants, and those undergoing high-risk procedures with known risk for hemodynamic instability or complications (e.g., ductal stenting, ductal closure in preterm infants, dilation and stenting of PVSs, dilation of peripheral PA stenoses, or VSD closure or creation). Other indications include patients with limited reserve for whom the planned procedure or effects of sedation may precipitate hemodynamic or respiratory collapse, need for transesophageal echocardiography, an anticipated lengthy intervention, risk of sudden movement (e.g., coughing during a PA or aortic intervention), or risk for hemoptysis, pulmonary edema, or postprocedural intubation. Beyond providing a potentially more steady-state condition than sedation with a natural airway, GETA also allows for more specific titration of ventilation, oxygenation, and other adjuncts like iNO. At our institution, the majority of our patients are managed with GETA – whether for diagnostic or interventional catheterization. General anesthesia with a laryngeal mask airway (LMA) is most often used for the stable patient status post heart transplant presenting for endomyocardial biopsy. Hemodynamics are supported by ensuring euvolemia, maintaining relatively light levels of anesthesia (0.5–1 MAC isoflurane), and starting low-dose vasopressors or inotropes as needed to counteract anesthetic-induced reductions in SVR and contractility. In high-risk patients, vasoactive agents are often started prior to induction. A second IV is routinely placed if the risk of bleeding is high or vasoactive initiation is anticipated. The latter can be done safely assuming that the site is monitored (either by direct visualization or indirectly by placing a pulse oximeter on that extremity) and that the lowest concentration vasoactive is used for a given patient weight.

Regardless of the anesthetic technique used, fundamental goals include minimizing pain and anxiety and providing conditions that allow for the accurate interpretation of the patient's hemodynamics. Premedication is often needed to achieve parental separation, particularly for those children and adolescents who present at frequent intervals. Oral midazolam (0.7 mg/kg), ketamine (3–5 mg/kg), or intranasal dexmedetomidine (2–3 mcg/kg) are effective for those without IV access. Following induction, every attempt is made to recreate and maintain the patient's baseline conditions for oxygenation, ventilation, and hemodynamics. To that end, patients are placed on room air or their baseline level of oxygen support, and a minute ventilation consistent with their normal ventilation is targeted. Because oxygen is a potent pulmonary vasodilator and hypoventilation or hyperventilation directly influence PVR, alterations in these variables can affect intracardiac pressure measurements and $Q_p : Q_s$ calculations. Such changes should, therefore, be avoided if possible during the diagnostic portions of the case. An equally important variable to control is pH. Acidosis, whether from a respiratory or metabolic cause, increases PVR. While respiratory acidosis is easily corrected if using mechanical ventilation, some amount of hypoventilation is to be expected with sedation techniques. Metabolic acidosis may indicate a low cardiac output state or the effects of prolonged fasting. The former can be diagnosed based on the patient's underlying condition, point-of-care ultrasound, or monitored values such as mixed venous saturation, lactate, or cerebral oximetry. While definitive treatment is initiated, metabolic acidosis can be addressed in the short term with sodium bicarbonate, assuming an adequate minute ventilation. Lastly, maintaining a sufficient depth of sedation or anesthesia is critical to minimizing intraprocedural hemodynamic swings associated with pain or anxiety that may affect the values measured/calculated. If the patient's condition requires an increase in oxygen levels or the initiation of vasoactive agents while measurements are being made, these changes should be communicated with the cardiologist such that the data obtained can be interpreted accordingly or be repeated after the patient has returned to baseline conditions.

Anesthetic drugs

Almost any anesthetic drug can be used safely provided an understanding of its impact on hemodynamics, synergistic effects with other sedatives and analgesics, and potential for adverse effects on a given patient's physiology (Table 34.13). Factors affecting choice of drugs include the child's myocardial function, comorbidities, and anesthetic plan.

For those patients undergoing sedation with a natural airway, combination of midazolam, fentanyl, ketamine, propofol, and/or dexmedetomidine has been used. Whereas midazolam or fentanyl may be sufficient for the cooperative adolescent or adult, a deeper level of sedation that often becomes a general anesthetic with a natural airway is most often required for younger patients. Common pairings include propofol and ketamine or ketamine and dexmedetomidine [153–156]. Regimens describing the former entail a bolus of propofol (1 mg/kg) and ketamine (1 mg/kg),

Table 34.13 Hemodynamic effects of anesthetic agents used for diagnostic or interventional catheterizations

	SVR	PAP	PVR	Dosing
Volatile	↓↓	↓	↓	0.5–1 MAC
Propofol	↓↓	↓	↓	1–3 mg/kg 100–300 mcg/kg/min
Ketamine	↑	↔↑	↔↑	1–2 mg/kg 0.3–1 mg/kg/hour or 5–20 mcg/kg/min
Dexmedetomidine	↑	↔	↔	0.25–1 mcg/kg (over 10 minutes) 0.2–1 mcg/kg/hour
Midazolam	↔	↔	↔	0.5–0.7 mg/kg PO 0.1 mg/kg IV in children
Fentanyl	↔↓	↔	↔	1–2 mcg/kg

Source: Modified from Lam et al. [152] and Twite and Friesen [33].

followed by an infusion of each (100 mcg/kg/min of propofol and 1 mg/kg/hour of ketamine) with rescue doses of 0.5–1 mg/kg ketamine as needed. Sedation with ketamine and dexmedetomidine involves a similar approach to ketamine dosing with the addition of dexmedetomidine at a load of 1 mcg/kg followed by an infusion of 1 mcg/kg/hour. When comparing these two approaches, the combination of ketamine and dexmedetomidine appears to be associated with a more frequent need for ketamine rescue doses and a longer recovery time. Alternative sedation strategies can entail dexmedetomidine infusions with or without a loading dose supplemented with midazolam for sedation and ketamine and/or fentanyl timed to the stimulating portions of the case. Ketamine and dexmedetomidine – independent of one another – have also been described as the sole agents used successfully for catheterizations [157–159]. Clinical experience suggests that such an approach is usually inadequate, though, and additional sedative and analgesic adjuncts are needed. For those patients who may be marginal, or in whom propofol or dexmedetomidine may be relatively contraindicated, ketamine with midazolam alone has proven effective.

Caveats regarding the use of propofol, ketamine, and dexmedetomidine during sedation focus on their hemodynamic profiles and side effects. Airway obstruction and apnea with subsequent oxygen desaturation and hypercapnea are more likely with propofol. Attention to airway patency and adequacy of respiratory rate and tidal volumes is essential when using it as an infusion. Decreases in SVR, myocardial contractility, heart rate, and blood pressure also pose a concern. Ketamine, with its increase in sympathetic stimulation, can balance these hemodynamic effects, but caution should still be used with propofol dosing and titration in patients at risk for myocardial ischemia or low cardiac output (e.g., AS, depressed ventricular function, and systemic-to-suprasystemic PH).

Controversy regarding the effects of ketamine in patients undergoing catheterization previously revolved around its effects on mPAP, particularly in patients with PH. But in the absence of hypoventilation or desaturation, ketamine does not appear to cause clinically significant increases in mPAP, PVRi, or PVRi/SVRi [34, 157]. Dysphoria, increased salivation, prolonged recovery, and nausea may, however, occur. Glycopyrrolate (5–10 mcg/kg) may be considered prophylactically for secretions if the patient can tolerate the potential increase in heart rate, whereas a propofol infusion may negate its other side effects.

Concerns regarding dexmedetomidine include its effects on myocardial conduction and potential for either systemic hypertension or hypotension when given as a bolus. In patients who may be at risk for or who have existing heart block or bradycardia, the use of dexmedetomidine may result in a worsened bradyarrhythmia [160]. Caution with dexmedetomidine should also be demonstrated in heart transplant patients presenting in the setting of hemodynamic evaluation for rejection. Schwartz et al. presented such a patient with a history of SVT and first-degree heart block who had a bradycardic arrest following a repeat bolus of dexmedetomidine [11]. The authors hypothesized that while dexmedetomidine was likely the causative agent, a combination of the patient's underlying first-degree heart block and possible acute cellular rejection involving the conduction system could have contributed as well. The use of dexmedetomidine in pediatric heart transplant patients who are otherwise well and with no significant or recent history of rejection appears safe. A group of 12 such patients were given a rapid IV bolus of either 0.25 or 0.5 mcg/kg over 5 seconds, resulting in transient but significant increases in systemic and pulmonary pressure with a more persistent decrease in heart rate [161]. The lowest heart rate observed was 71 at 5 minutes following administration. When assessing the effects of dexmedetomidine on patients with PH, loading doses as high as 1 mcg/kg given over 10 minutes were not associated with statistically significant increases in PAP [33]. Of note, while the most common hemodynamic effects of a loading dose of dexmedetomidine are hypertension and bradycardia, hypotension and a decrease in cardiac index may also result. Particular caution is warranted, then, when considering boluses in those who may be depleted of catecholamines, such as patients in heart failure. A strategy to consider in all cardiac patients is to administer a smaller loading dose over a longer period of time to allow for evaluation of hemodynamic effect (0.25–0.5 mcg/kg over 10 minutes, which can be repeated if needed).

If GETA is planned, myocardial function often dictates whether an inhalation induction with sevoflurane can be used versus an IV induction. For patients with even moderately depressed ventricular function, low-dose sevoflurane (2–3%) can be used for induction provided that IV access is quickly obtained. IV induction using a balanced technique of opioids, benzodiazepines, ketamine, muscle relaxant, and/or inhalational agent is most reasonable in patients with severely depressed function. More important than the drugs chosen, though, are the doses used and careful titration to effect while monitoring hemodynamics. Maintenance can be achieved with isoflurane at 0.5–1 MAC. Adjuncts like dexmedetomidine have been used to minimize the concentration of volatile agent needed, but may not confer any hemodynamic advantage compared to general anesthetics in which it is not used [162]. Chapter 10 presents additional information about anesthetic agents in CHD.

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Monitoring

Monitoring used in the CCL is comparable to that in the operative setting with a few notable differences. Standard ASA monitors are routinely employed using a five-lead EKG, noninvasive blood pressure cuff, esophageal temperature probe, and pulse oximetry. The utility of the EKG and blood pressure monitoring, however, depends on placement. The use of radiopaque EKG leads and cables necessitates lead placement away from the chest and commonly onto the arms to avoid obstructing views of the heart during fluoroscopy. While gross arrhythmias or ischemic changes can be detected in this configuration, the use of radiolucent EKG leads and cables that allow for anatomic placement over the chest offer better diagnostic capability (Figure 34.24). Likewise, the placement of a noninvasive blood pressure cuff on an upper extremity that is then positioned with the arms above the head may occasionally result in lower than actual blood pressure readings. In infants and small children, an alternative may be to place the cuff on the lower extremity not being accessed for the procedure. Respiratory rate and end-tidal CO_2 ($ETCO_2$) are additional monitoring constants and are followed using capnography in both intubated and sedated patients. For sedated patients, the $ETCO_2$ sampling line can be placed either onto a nasal cannula designed to allow such monitoring or under a face mask using an angiocatheter.

Other monitors to consider on a case-by-case basis include a peripheral arterial line, cerebral oximetry, and a Foley catheter. For most procedures, the interventional cardiologist accesses the femoral artery, which can be used for blood pressure monitoring. A separate arterial line, however, may be indicated in at-risk patients for the following reasons: (i) if closer assessment of blood pressure is desired in the peri-induction period; (ii) if the arterial access placed by the interventionalist is to be used for the intervention itself (and therefore would not be available for monitoring); or (iii) if postprocedural hemodynamic instability or blood gas sampling are anticipated. Cerebral oximetry may help in assessing changes in cardiac output and determining transfusion thresholds in critically ill patients. Common indications for a Foley catheter include either an anticipated lengthy procedure or one associated with the need for diuresis (e.g., pulmonary vein interventions).

Though not considered traditional anesthesia monitors, information obtained from arterial blood gases (ABG) and measurements of ACT are also essential to patient management. An ABG is sent with initial arterial access to assess the child's acid–base status, hematocrit, and oxygenation/ventilation. Thereafter, ABGs may be sent infrequently. If the patient's clinical situation dictates that another ABG be sent, a gentle reminder to the cardiologist may be needed. A common practice is to send an ABG along with the ACT so that trends can be followed. ACTs are checked at routine intervals when heparin is administered and is reflective of the patient's level of anticoagulation. Heparin can be administered as a bolus (50–100 units/kg) alone or as part of the flush used to maintain catheter patency. In the latter circumstance, rising ACT values may indicate significant heparinization secondary to large volume flush administration. A protocol-driven approach to heparin and ACT management is desirable; at Texas Children's Hospital, for example, ACT is measured every 30 minutes after heparinization; target ACT is 250 seconds when the left side of the heart or systemic circulation is entered, e.g., transseptal puncture for left atrial access or retrograde access to the aorta.

Equally important to the above data is an understanding of where catheters are within the body at any given time and what potential hemodynamic effects their movements or actions (e.g., balloon inflation) can cause. This information is critical to interpreting hemodynamic changes and anticipating critical events. Direct visualization of these aspects, however, is difficult in the CCL. There are physical barriers to communication and visualization, including lead screens and the lateral cameras. Risk of radiation exposure also increases with proximity to the cardiologist, often leading to the anesthesiologist being at a distance from the cardiology team. Moreover, the monitors displaying fluoroscopy images and intracardiac pressures that allow for an exact understanding of what is happening may be either remote or



(A) (B)

Figure 34.24 Radiolucent electrodes and cables. (A) Examples of radiolucent electrodes (MedGel® and SilverTRACE®) and cables (Vyaire™ Multi-Link EKG Leadwire) used to allow anatomic positioning in the cardiac catheterization laboratory. (B) Comparison of standard radiopaque electrodes and cables (solid arrows) to radiolucent ones (dotted arrow) on lateral fluoroscopy of the heart. Note that the cable attached to the radiolucent lead is not even visible.

entirely out of view from the anesthesiologist. These challenges underscore the need for excellent and interval communication between anesthesiology and cardiology (which at times requires interrupting the procedure). A convincing argument could be made that the ability of the anesthesiologist to view fluoroscopy and hemodynamic data is a patient safety issue, and arrangements should, therefore, be made to allow these monitors to be viewed from the anesthesiology work area. In patients who experience acute desaturations or altered lung compliance, fluoroscopy is particularly useful to assess ETT position and to rule out the presence of pulmonary edema or hemorrhage.

Intravascular volume management

Patients undergoing catheterization are inherently at risk for volume overload by both the anesthesiologist and the cardiologist [145]. For the anesthesiologist, efforts should be made to limit IV fluids, except when indicated in the setting of hypovolemia, bleeding, or instability. A Buretrol® filled to a predetermined level can effectively minimize the risk of inadvertent large volume administration in smaller and younger patients. A more common (and less immediately obvious) cause of hypervolemia is the cumulative effect of intermittent and occasionally rapid infusions of flush and contrast. Clinical consequences include hemodilutional anemia, electrolyte abnormalities, pulmonary edema, and decreased myocardial function due to myocardial stretch. Those at greatest risk are neonates and infants due to their smaller blood volumes and patients otherwise with already depressed ventricular function. Attention to worsening lung compliance, increases in measured ACT independent of heparin boluses (because flush and contrast may also contain heparin), and profuse increases in urine output are common signs of volume overload. Serial blood gases should also be monitored to assess for the impact on hemoglobin and electrolytes. Rarely, transfusion is needed to increase hemoglobin levels. More commonly, IV diuresis (furosemide 1 mg/kg) and time are the only treatments needed. In the event that oxygenation or ventilation is impaired, postprocedural mechanical ventilation is indicated to allow more time for diuresis.

Other causes of anemia include blood loss from attempts at vascular access and sheath/catheter exchanges, and blood sampling for oxygen saturations, ABGs, and ACTs [145]. Blood loss can be insidious. The drapes around the groins are often stained with blood, but it is difficult to use this alone as a marker of blood loss. Much of the administered flush can collect on the drapes and mix with any blood present, giving the appearance of more significant bleeding than is actually present. Trending the patient's hemodynamics and assessing hemoglobin on serial ABGs is one approach to assessing for anemia. As for any patient, the threshold for transfusion should depend upon the patient's underlying physiology and an assessment of the adequacy of oxygen delivery and end-organ perfusion. Whereas a noncyanotic and otherwise healthy child may well tolerate a hemoglobin of 7 g/dL, a cyanotic patient accustomed to a higher hemoglobin almost certainly would not. Cerebral oximetry can be used as a surrogate of end-organ perfusion and adds another data point in the decision of whether or not to transfuse.

Recovery

Stays in the recovery room following catheterization are much longer than that for other anesthetics. The time frame can range from 2 to 6 hours and is directly related to the risks of bleeding and hematoma formation from the vascular access sites. Efforts to minimize these complications include keeping the child supine and relatively immobile for the first few hours postcatheterization. Long-acting sedation and analgesia along with the avoidance of emergence delirium and PONV can be helpful in achieving this goal (particularly in younger children for whom laying still is an oxymoron). Gautam et al. studied the effects of dexmedetomidine for this purpose in children between 1 month and 5 years of age who underwent catheterization. When given as a bolus of 1–2 mcg/kg prior to deep tracheal extubation with sevoflurane (0.8–1 MAC), 91% of patients had a documented smooth recovery requiring no additional analgesics or sedatives [163]. Such an approach, or a comparable one using propofol in those can tolerate its negative hemodynamic effects, may limit postprocedural bleeding associated with movement, coughing, or agitation. While the cardiologist most often infiltrates the access site with local anesthetic at the end of the case, systemic opioids like morphine may be needed particularly if large sheaths are used (e.g., for TPVR placement). Of note, routine deep tracheal extubation requires that the recovery nursing staff be familiar with the airway complications that may occur in this setting and also maneuvers to temporize until help arrives. A pathway for calling for help and the immediate availability of emergency drugs in the recovery room can help ensure a prompt response should an event like laryngospasm occur.

KEY POINTS: ANESTHETIC MANAGEMENT

- Risk reduction begins prior to arrival in the CCL with preprocedural medication management and scheduling such as to avoid lengthy NPO times or concurrent illnesses.
- Preprocedural checklists are useful to identify key anesthetic and cardiology concerns and to ensure the availability of necessary personnel and resources.
- GETA should be considered in neonates, infants, and those patients otherwise undergoing high-risk procedures.
- Monitoring in the CCL involves an assessment of serial ABGs, ACTs, and the position of catheters within the heart in addition to the usual vital signs.
- Recovery can last for several hours due to the need to monitor for access site bleeding.

Electrophysiology procedures

The most common procedures performed in the EP suite are electrophysiology studies (EPSs) and ablations for the management of tachyarrhythmias. Less common are implantation of pacemakers and/or defibrillators, cardioversion, and lead extraction.

Electrophysiology studies and ablations

The purpose of an EPS is to identify the mechanism of the patient's arrhythmia by recording signals from electrodes placed within the heart. The use of fluoroscopy and correlation of electrical signals to anatomic landmarks allow localization of the abnormal pathways or foci responsible for the arrhythmia. Ablation of these pathways is then pursued and is initially successful in 91% of patients with a recurrence rate of 23% [164, 165].

The majority of children presenting for EPSs and ablation are otherwise healthy, have functionally normal hearts, and present with well-tolerated SVT. A minority will have either a life-threatening arrhythmia or an arrhythmia complicating CHD (7.9%) or cardiomyopathy (2.4%) [166]. Anesthetic concerns include the length of the procedure, poor access to the patient, the possibility of anesthetic agents altering the EP of the heart, and occasionally poor cardiac function. Chapter 22 presents an extensive discussion of arrhythmias.

Pathogenesis of arrhythmia

The most common mechanism of tachycardia is reentry, of which atrioventricular nodal reentry tachycardia (AVNRT) is the most common example. This requires a circuit composed of two pathways with different conduction velocities and refractory periods. In AVNRT, the normal AV node receives an input from two physiologically distinct pathways: a slow pathway conducting slowly with a short refractory period and a fast pathway that conducts quickly with a longer refractory period. Normal conduction occurs via the fast pathway. If an ectopic beat reaches the two pathways while the fast pathway is refractory, the impulse is conducted via the slow pathway only. In some individuals, the conduction speeds and refractory periods of the two pathways are such that tachycardia is perpetuated due to a circuit comprising anterograde conduction via the slow pathway, retrograde conduction via the fast pathway, and conduction through the atrial myocardium. Preexcitation syndromes, such as Wolff-Parkinson White (WPW), are a subgroup of reentry tachycardia in which one arm of the circuit is the AV node and the other is a congenital muscular pathway between the atrium and the ventricle [167]. Such accessory pathways can originate in either the right or left atrium.

Another mechanism of tachycardia is enhanced automaticity. During sinus rhythm, cells in the sinoatrial (SA) node function as the heart's pacemaker by independently generating rhythmic impulses through spontaneous depolarization. Other cells demonstrate this activity but at a slower rate and will only act as the pacemaker if the SA node is not functioning or conduction is blocked. When these cells are damaged or subjected to extrinsic factors (electrolyte disturbance, hypoxia, hypercarbia, high wall tension, ischemia, and high catecholamine levels), they may spontaneously depolarize at a rate that supersedes the SA node. This leads to rapid repetitive depolarization of a single focus, referred to as ectopic or automatic tachycardia.

Ventricular tachycardias (VTs) and premature ventricular beats (PVCs) are relatively uncommon in the pediatric population. In patients with structurally normal hearts, the most common types are fascicular tachycardia and automatic tachycardia originating in the outflow of the RV. Fascicular VT occurs due a reentry circuit involving the left bundle branch. In patients with operated CHD, VT may occur due to reentry circuits around scar tissue. This is more commonly seen in adults than in pediatric patients.

Electrophysiology techniques

Figure 34.25 demonstrates typical catheter position during an EPS for investigation of SVT.

The electrical signals detected by these catheters can be correlated with anatomic location using electroanatomic mapping systems to produce a three-dimensional representation of the heart. This technology can enhance the safety and efficacy of ablations by providing the precise location of the catheter relative to critical cardiac structures and by creating a visual marker of areas to be ablated (Figure 34.26). An additional benefit of such systems is the decreased need for fluoroscopy and decreased radiation exposure [168].

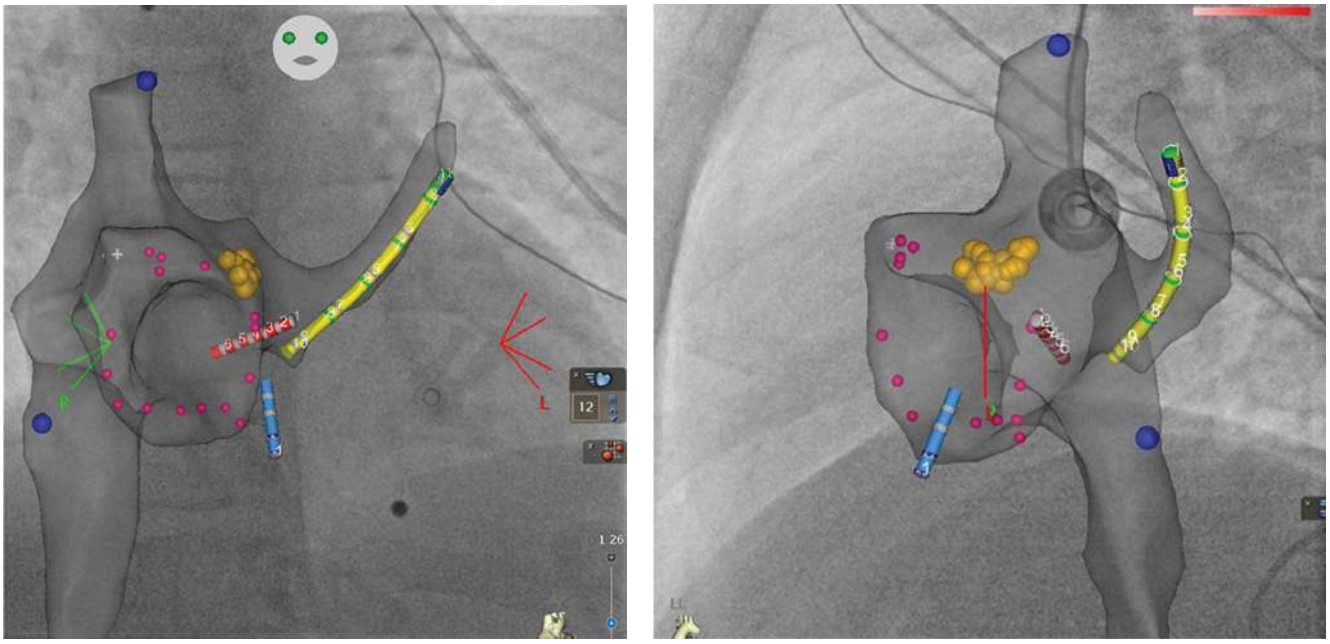
To identify the mechanism of the arrhythmia, periods of pacing and programmed stimulation are undertaken. Pacing, commonly via the coronary sinus, allows the arrhythmia to be provoked or terminated, permits measurement of the EP properties of the conduction system, and allows for ventricular pacing should CHB occur. Drugs may be used to further refine the study. Adenosine will block normal AV conduction, exposing a concealed abnormal pathway. Isoproterenol, in contrast, will increase SA node rate, speed up AV node conduction, reduce refractory periods, and increase automaticity of other contractile tissue.

Radiofrequency ablation and cryoablation

Destruction of an accessory pathway, the slow pathway of an AVNRT, or automatic foci abolishes the arrhythmia. This is most often accomplished by delivering RF energy to heat and ablate the area. An alternative to RF catheter ablation (RFCA) is cryoablation, the freezing of the foci. This allows for the pathway or foci to be temporarily disabled prior to its destruction. This can be a safer option when the pathway is close to the AV node, such as in AVNRT. In the treatment of preexcitation syndromes, a specialized catheter is positioned along the AV ring, then adjusted to record the earliest conduction via the abnormal pathway (Figure 34.26). When delivering RF energy, the size of lesion created is dictated by the power. Temperature control is used to stop overheating of local tissue and blood. Following ablation, an EPS is repeated to test for residual or additional pathways.

Complications and risk factors with electrophysiology studies

MAEs associated with EPSs and tachyarrhythmia ablations are rare, approximating 0.1% in a recent cohort [169]. Apart from hematomas or injury otherwise associated with vascular access, complications are largely related to ablation attempts and transseptal puncture for left-sided arrhythmias. RFCA can cause acute coronary occlusion or stenosis when performed in proximity to the AV junction [170]. Other complications include arrhythmias requiring cardioversion, AV block requiring temporary or permanent pacemaker, right or left bundle branch block, thromboembolism (stroke),



(A) (B)

Figure 34.25 Electroanatomical map overlying fluoroscopic images of the heart. (A) Anteroposterior view of mapping catheters in the coronary sinus (yellow), right ventricle (blue), and His (red) positions. The catheter in the coronary sinus is multipolar and, therefore, capable of detecting signals along its length. This catheter allows for analysis of left-sided electrical conduction without having to directly access the left atrium/ventricle. The blue circles denote the transition between the electrically inert superior and inferior venae cavae and the electrically active right atrium. The tricuspid annulus is marked by pink circles and the His by yellow circles. (B) Lateral view. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory, Dr. Taylor Howard.)

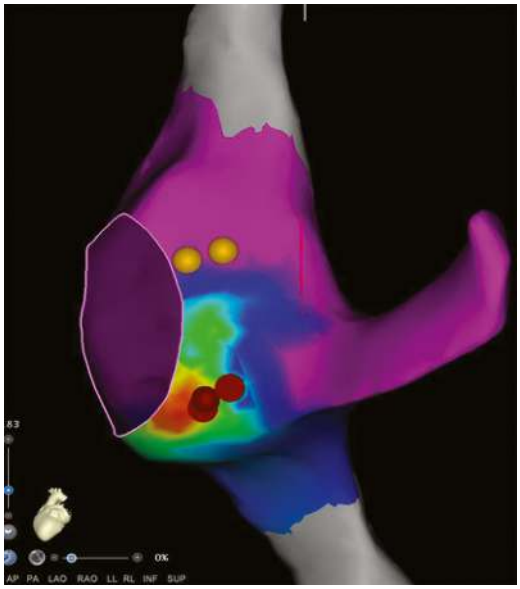


Figure 34.26 Local activation time map highlighting areas of interest for ablation. Accessory pathways such as those in this patient with Wolf-Parkinson White (WPW) syndrome are characterized by electrically conductive fibers, which cross the electrically inert atrioventricular valve. The insertion of this fiber creates a unique signal that, when mapped, appears to be "early" compared to other signals on the valve. All signals are compared to a reference point (in the case of WPW, usually the delta wave of the QRS complex). As the catheter is move around the valve, a color map is created with earlier signals being denoted in red and the later signals in purple. The red circles denote areas of ablation. (Source: Texas Children's Hospital Cardiac Catheterization Laboratory, Dr. Taylor Howard.)

AVV injury, cardiac perforation, pericardial effusion, and tamponade. Risk factors associated with adverse events are younger patient age (infants) and lower weight (<15 kg), patients with CHD, patients undergoing VT rather than SVT ablation, and centers with low ablation volumes [171–173].

The child younger than 4 years presenting for ablation often indicates a significant arrhythmia not controlled by antiarrhythmic drugs. There have been recent reports of successful ablation in children as young as 1 month of age, but complications are more common [171, 174, 175]. Such patients will frequently have abnormal ventricular function and severe refractory arrhythmia prior to an EPS being contemplated.

Patients with CHD may develop arrhythmia in a number of circumstances [168, 176]. Ebstein's anomaly is associated with accessory pathways and preexcitation. Atrial dilation and scarring within the heart may occur secondary to surgical palliation or repair and is often associated with arrhythmia. The latter is especially true following extensive atrial surgery, such as the Mustard procedure or classical Fontan connections. Adults with TOF with long-standing pulmonary insufficiency may also present with RA and RV enlargement with either atrial or ventricular arrhythmias. This group of patients may have poor reserve to tolerate tachycardia, and placement of intracardiac electrodes may be complex.

Anesthetic considerations

As with other catheter-based procedures, it is possible to conduct EPSs in conscious patients or with minimal sedation. These procedures are often hours in length, however, and can require multiple venous and arterial access points.

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Periods of arrhythmia are inevitable and can be unpleasant for the patient. Moreover, movement during the procedure can disrupt the electroanatomic map and interfere with catheter stability and myocardial contact during ablation. The latter diminishes the effectiveness of ablation lesions and may also increase the risk of injuring adjacent structures [169, 177–182]. Deep sedation is unlikely to offer any advantage to general anesthesia, and the additive effect of repeated doses of sedative drugs over a period of time must be considered. Consequently, our practice is to use GETA unless the patient's underlying arrhythmia (PVCs or VT), or prior history of failed ablation, suggests a benefit to conscious sedation.

Preprocedural evaluation entails assessment of the frequency of the arrhythmia, precipitating factors, symptoms during the arrhythmia, and whether treatment is required for termination. Arrhythmias associated with fainting or collapse are likely to be associated with greater hemodynamic compromise. Equally important is the mechanism of the arrhythmia. Certain mechanisms, noted below, are more susceptible to anesthetic depth (and specific agents) than others. Tailoring the anesthetic to the anticipated arrhythmia may avoid a failed ablation or an unnecessarily lengthy procedure due to difficulty in eliciting the arrhythmia. Discussion with the electrophysiologist can identify those patients who require either a lighter plane of anesthesia or minimal sedation initially to facilitate arrhythmia induction.

Though the majority of patients are otherwise young and healthy, the presence of CHD, cardiomyopathy, or familial conditions associated with arrhythmia (long QT syndrome and arrhythmogenic RV dysplasia) may confer increased risk. Adults with CHD presenting for ablation are often in compensated heart failure due to long-standing arrhythmias and poor ventricular function. Further, those adults with rate-controlled atrial arrhythmias may be managed on anticoagulants to decrease their risk of stroke. While these medications are usually held in advance, the decision is made weighing the risks of procedural bleeding with their continued administration versus that of stroke with stopping them. Antiarrhythmics are commonly held several days prior to the procedure. Anxiolysis with midazolam can be helpful in children and adolescents due to the increased time between separation and induction (needed to allow placement of the posterior surface electrodes used for electroanatomic mapping).

Standard monitors and the use of defibrillation pads are routine. Additional vascular access including a dedicated arterial line and a separate site for vasoactive infusions is infrequently needed, but placed as indicated in at-risk patients. If using GETA, a Foley catheter is used as average case lengths approach 4–6 hours. X-ray tables are firm, and patient positioning can be awkward. Care must be taken to avoid injury to nerves and pressure areas.

Periods of tachycardia (either due to arrhythmia or due to pacing) are to be expected during an EPS and healthy patients tolerate this well. Significant hemodynamic compromise can occur, however, with very high ventricular rates or in patients with reduced cardiac reserve. Vasopressors may be used to improve perfusion pressure but can have reflex effects on the EP of the heart (e.g., bradycardia with phenylephrine). Alternatively, vasopressin can be used. Nonpharmacologic interventions entail communication with the electrophysiologist so that the arrhythmia can be terminated rapidly by overdrive pacing, or if the cause of instability is pacing itself, the pacing can be stopped to allow recovery and time for volume/vasoactive management. Adenosine or external cardioversion is rarely required to treat arrhythmias. A common practice in patients who can tolerate the volume load is to administer a fluid bolus with the start of the procedure to ensure euvolemia and minimize the risk of hypotension with the onset of arrhythmias and/or pacing. Adenosine and isoproterenol, used to define and elicit arrhythmias, can also induce hypotension. Importantly, in patients with a history of reactive airways, adenosine can provoke bronchospasm [183].

If the abnormal pathway or foci is left sided, the left atrium is accessed via transseptal puncture, most commonly from the RA. Changes in heart rate or blood pressure with this approach require further evaluation as tamponade is a known complication [184]. As noted above, additional heparin 50–100 units/kg with a target ACT of 250 seconds is often employed in this setting to decrease the risk of thromboembolism.

PONV in children undergoing ablation is unfortunately common with a reported incidence of 7–63% [185, 186]. Because the use of dexamethasone as an antiemetic may hinder scar formation following ablation, alternative agents for PONV prophylaxis including subhypnotic infusions of propofol (10–100 mcg/kg/min) and ondansetron should be considered. Lee et al. reported that infusions of propofol <100 mcg/kg/min were associated with a decrease in postprocedural vomiting, but not nausea, following ablation [185].

Anesthetic drugs and the cardiac conduction system

All anesthetics influence the electrical conduction of the heart. In the context of an EPS, the relevant question is whether the agents used will inhibit the induction of the targeted arrhythmia (and thereby prevent its characterization, localization, and ablation). The answer appears to depend less on the specific drugs administered, and more on the mechanism of tachycardia. Reentry tachycardias are least affected by common anesthetic agents, whereas automatic tachycardias are highly susceptible to the suppressive effects of anesthesia. As such, while any number of drugs can be used successfully in the anesthetic management of a child undergoing WPW or AVNRT ablation, greater caution may be needed to allow arrhythmia induction in the child with ectopic atrial tachycardia (EAT) or automatic VT.

Anesthetic drugs and reentry tachycardias

Many anesthetic agents have been used successfully in the ablation of reentry tachycardia, including various combinations of volatile agent, midazolam, fentanyl, remifentanil, propofol, ketamine, and even dexmedetomidine. As arrhythmia inducibility is less critical to the successful ablation of WPW [169], anesthetic choices for this lesion are broad. More caution has been advised when managing children with AVNRT, but similar rates of success in terms of arrhythmia induction have been noted regardless of the anesthetic technique (GA vs. MAC) or drugs used [169]. A summary of the electrophysiologic effects of common anesthetics and their impact of SVT inducibility is described in Table 34.14 [187].

Table 34.14 Electrophysiologic effects of common anesthetics during SVT ablation

Anesthetic sedative	Effect on AV node conduction	Effect on induction of SVT	Comments
Volatile anesthetics	↔↓	↔	Isoflurane and sevoflurane used successfully
Midazolam	↔	↔	Minimal clinical effect.
Fentanyl	↔↓	↔	Minimal clinical effect. May cause vagal-mediated bradycardia.
Remifentanil	↓	↔↓	Induces bradycardia and has potential to inhibit SVT induction at high doses, but has been used successfully
Propofol	↔	↔	Commonly used but caution in EAT
Ketamine	↔↑	↔↑	May counteract depressive effects of dexmedetomidine
Dexmedetomidine	↓	↓	Controversial. May require additional doses of isoproterenol to elicit arrhythmia; may confound etiology of heart block with RFCA near AV node. Caution in EAT.

Source: Modified Vladinov et al. [187].

↔, no significant clinical effect on conduction or induction of SVT; ↑, speeds conduction and promotes induction of SVT; ↓, slows conduction and inhibits induction of SVT; AV, atrioventricular; EAT, ectopic atrial tachycardia; RFCA, radiofrequency catheter ablation; SVT, supraventricular tachycardia.

Though volatile anesthetics have been demonstrated to slow the SA node and prolong AV conduction time and refractoriness, these findings do not appear to be clinically significant [186–189].

Midazolam has no effect on normal AV or accessory pathway conduction and no important clinical effect on SA node activity [186, 190, 191].

Of the opioids, fentanyl can induce vagally mediated bradycardia but does not adversely affect arrhythmia induction with either boluses or infusions [190]. The combination of fentanyl and midazolam has similarly inconsequential effects on EP variables [192, 193]. Remifentanil is more controversial. At high-dose (0.4 μg/kg/min) and moderate-dose (0.2 μg/kg/min) infusions, remifentanil prolongs the sinus node recovery time, and at the high dose, also suppresses sinus node automaticity [194]. Niksch et al. reported slowing of both SA and AV node conduction at doses of 0.3 mcg/kg/min [195]. These effects may lead to difficulty in inducing arrhythmias, but other groups have demonstrated successful use with doses of up to 0.2 mcg/kg/min in patients undergoing general anesthesia [189, 196]. If using remifentanil, its short context-sensitive half time makes stopping an infusion an option if difficulty arises in eliciting the arrhythmia.

Propofol has minimal to no effect on the SA and AV nodes, intra-atrial conduction, or characteristics of the accessory pathway even at doses of 200 mcg/kg/min [186, 189, 195, 197, 198]. Likewise, ketamine has no significant effect on SA or AV node function but can induce significant increases in heart rate and blood pressure due to its stimulatory effects on the sympathetic nervous system. Its use may be beneficial, then, in patients with preexisting bradycardia or hypotension [189].

Dexmedetomidine induces depression of both the AV and SA nodes and consequently may adversely affect the inducibility of arrhythmias [160]. Tirotta et al., however, concluded that dexmedetomidine does not interfere with EPSs for SVT in their retrospective review of 405 cases between 2007 and 2014 [199]. Three groups were studied: (i) those with no exposure to dexmedetomidine, (ii) those given an infusion of 0.5–1 mcg/kg/hour, and (iii) those given a bolus of 0.5 mcg/kg, followed by an infusion of 0.5–1 mcg/kg/hour. No differences were noted among the groups in terms of SVT inducibility or recurrence, but patients receiving dexmedetomidine did require additional doses of isoproterenol to induce SVT. Char et al. demonstrated that ketamine may also counteract the electrophysiologic effects of dexmedetomidine [200]. Both ketamine and isoproterenol act as sympathetic agonists, and in doing so, may mitigate the negative chronotropy caused by dexmedetomidine. Beyond dexmedetomidine's effects on SVT inducibility, an additional consideration that may impact its use is its potential to confound the etiology of heart block should it occur. CHB is an exceedingly rare complication, but would be most relevant in a child undergoing AVNRT ablation due to the involvement of the AV node.

Anesthetic drugs and automatic tachycardias

Arrhythmias resulting from increased automaticity, such as EAT or VT, can be more difficult to elicit under anesthesia. Many of the extrinsic factors that promote automaticity (such as elevated catecholamine levels) are minimized during an anesthetic. These changes make the choice of anesthetic critical in these patients.

In a comparison of outcomes of pediatric ablation procedures by anesthesia strategy (GA vs. MAC), the use of GA was associated with a higher rate of noninducibility (and therefore nonablation) in children with PVCs or VT [169]. In this group, GA increased the likelihood of a negative EPS with an OR of 2.2. For patients with EAT, however, the type of anesthesia used did not affect inducibility. The authors noted that a larger number of EAT cases were needed to definitively comment on this population. The most commonly used drugs for MAC were propofol, midazolam, and fentanyl, whereas propofol, volatile agent, neuromuscular blockade, fentanyl, and midazolam were most utilized for GA. Exact dosages and the depth of anesthesia obtained with MAC were not specified.

Lai et al. reported different findings in children with EAT who underwent a propofol-based anesthetic (induction with 200 mcg/kg/min followed by reduction to 100 mcg/kg/min) [201]. In four of seven children with EAT, the arrhythmia was

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terminated with propofol and could not be induced despite an infusion of isoproterenol.

Given these data, it is difficult to suggest a best anesthetic technique for EPSs in patients with automatic (ectopic) tachycardias. General suggestions, however, can be made. For cooperative older children or adolescents, an MAC approach may most reliably preserve the ability to induce arrhythmias and allow a successful ablation. In younger children or patients for whom MAC is not an option, GA can be maintained preferentially with lower doses of volatile agent. The expected loss of endogenous sympathetic activity with GA can be supplemented with isoproterenol.

KEY POINTS: ELECTROPHYSIOLOGY STUDIES

- The majority of children presenting for EPS and ablation are otherwise healthy, have structurally normal hearts, and present with well-tolerated SVT.
- More rare and higher risk are patients with CHD and those presenting for ablation in early childhood or infancy.
- A child with VT or EAT should prompt discussion as to whether sedation versus GA would be best to optimize successful arrhythmia induction and ablation.
- Adenosine is used in the assessment of arrhythmias and can produce bronchospasm in children with reactive airway disease or asthma.
- PONV is common following EPSs and should be managed prophylactically.

Implantation of pacemakers and defibrillators

Pacemakers in children are rare [202]. The most common indication is symptomatic bradycardia secondary to congenital or postsurgical AV block. Other indications include antitachycardia pacing for SVT or sinus node dysfunction in the setting of impaired cardiac output.

Leads can be delivered transvenously through the subclavian vein or placed epicardially through a subxyphoid approach (partial sternotomies and thoracotomies have also been used). These leads are then attached to a pulse generator, which is implanted in the SQ tissue of the chest (transvenous leads) or the abdomen (epicardial leads). Alternatively, the generator may be placed deep to the pectoralis or rectus abdominis muscles, respectively, in young or thin patients to minimize the risks of erosion and infection. Factors that influence the choice of transvenous versus epicardial systems include (i) the size of the central veins, (ii) amount of the SQ tissue at the implantation site, and (iii) whether or not the heart can be accessed through a transvenous approach. Smaller vein size is a risk factor for central venous thrombosis or obstruction when using transvenous leads. Consequently, epicardial leads are most often used in patients weighing <15 kg. Epicardial leads are also indicated in children whose hearts cannot be accessed via a systemic vein (e.g., Fontan circulation) or those with intracardiac shunts (due to the risk of systemic thromboembolism with transvenous leads). Challenges common to both systems include the continued growth of the child (relative to fixed leads) and the related issues of lead failure and fracture.

Most recently, leadless pacing systems have been introduced. As the descriptor suggests, neither leads nor a separate generator pocket is needed. Such devices are implanted transvenously into the RV myocardium as a self-contained unit, comprising the functionality of a lead and generator in one capsule that is 90% smaller than the typical pulse generator [203]. While promising in their ability to avoid the morbidity associated with transvenous and epicardial systems, leadless systems are currently restricted to older children and adolescents due to the large size of the transfemoral sheath needed for deployment. Such devices are predominantly used as single chamber ventricular pacemakers. Current indications for use are the need for backup pacing (those with intermittent pauses or block who need only occasional rather than continuous pacing) and those with venous occlusions that preclude standard pacing systems [204].

Children undergoing either epicardial or transvenous lead placement are managed with GETA, while adults who are cooperative can be managed with sedation and abundant local anesthesia. The induction of general anesthesia can occasionally lead to worsened bradycardia. Beta-agonists such as isoproterenol or epinephrine can be trialed to increase heart rate, or temporary pacing may be instituted (transcutaneously, transvenously via a pacing catheter, or transesophageally via an esophageal pacing probe). Regional anesthesia with pectoral nerve blocks may decrease postoperative pain and opioid consumption in patients undergoing subpectoral generator placement [205]. Periprocedural complications associated with transvenous approaches include vascular injury, myocardial perforation, and AVV injury. Acute lead dislodgement or failure can occur regardless of approach and is associated with traction with patient movement.

Implantation of implantable cardioverter-defibrillators (ICDs) is indicated for life-threatening cardiac arrhythmias [206]. Examples include isolated arrhythmia associated with long QT syndromes and patients with hypertrophic cardiomyopathy or arrhythmogenic RV dysplasia who may have more generalized myocardial disease [206–209]. CHD associated with ICDs include TOF, anomalous origin of the coronary arteries, transposition, and Ebstein's anomaly [206]. As with pacemakers, these devices can be placed either transvenously or epicardially [210]. SQ ICDs designed initially for adults are now also being applied in pediatric patients [211–213]. It is usual to test the defibrillator by induction of ventricular fibrillation and it is prudent to be prepared with external defibrillation pads and pharmacologic agents (as indicated by the pathophysiology of the arrhythmia) in the event the device fails. Often, patients present after near-miss sudden death or death of a close family member and can be extremely anxious. Preoperative anxiety can be sufficient to induce arrhythmia, and premedication with an anxiolytic is advisable.

Elective cardioversion

Patients presenting for elective (or nonemergent) cardioversion have stable tachyarrhythmias and are most often adults

with CHD. Atrial fibrillation and flutter (AF/F) are the most common indications, with some presenting for first-time cardioversion and others for breakthrough arrhythmia in spite of antiarrhythmic therapy. Due to the risk of thromboembolism with AF/F, patients are managed with anticoagulation in advance of cardioversion [214, 215]. For patients with AF/F of unknown duration or longer than 48 hours who have not been anticoagulated for the preceding 3 weeks, TEE is performed prior to cardioversion to rule out left atrial appendage thrombus.

Anesthetic concerns are related to patient and procedural factors. Key patient factors include the underlying cardiac diagnosis and current functional status. Long-standing arrhythmias can result in worsened cardiac function that can manifest clinically with signs of heart failure. Conversely, severely depressed function at baseline can serve as the nidus for arrhythmia. The presence of these findings indicates higher risk. Procedure-related factors include where the procedure is to be performed and whether or not TEE is needed. The former influences preparation, whereas the latter can dictate airway management and the choice of sedatives/anesthetics to be used.

Locations for elective cardioversion and/or TEE at our institution have included the EP suite, procedure room, and ICU. Each site has its pros and cons, but in those patients who are at highest risk for anesthesia-induced instability, a plan for resuscitation and the availability of essential personnel (surgeons and perfusionists) in the event of an arrest are likely more important than the location itself. If performing the procedure outside a normal anesthetizing site, usual precautions are taken to ensure the availability of all necessary equipment and drugs.

For patients who need TEE, we commonly secure the airway with an ETT. Of note, many adult institutions perform these procedures as MACs while maintaining a natural airway. Our choice for GETA is informed by the relative infrequency of this procedure (and therefore our inexperience with MAC in these cases), concern that hypoventilation or hypoxemia associated with MAC may result in instability in already tenuous patients, and the unpredictable length of TEE.

For patients presenting for cardioversion *without* TEE, a number of sedatives or anesthetics can be used while maintaining a natural airway. A recent Cochrane review found no consistent difference in safety, efficacy, or adverse events among the most commonly used agents: propofol, etomidate, sevoflurane, isoflurane, midazolam, and diazepam [216]. As with all CHD, the dose of the drug used rather than the drug itself is most relevant. Knowles described the administration of a slow bolus of propofol (0.5–1 mg/kg) with additional doses (0.25 mg/kg) as needed in those with severely limited cardiorespiratory reserve [217]. Phenylephrine or ephedrine can be used in conjunction with such boluses to mitigate the negative hemodynamic effects of propofol. Sevoflurane alone has also been reported as efficacious in high-risk patients [217, 218].

Transvenous lead extractions

Transvenous lead extraction is defined as the removal of a lead that has been implanted for greater than a year or that requires specialized extraction tools [219]. Patients presenting for this procedure are often adults (with a median age of 40 years at Texas Children's) who can have either structurally normal hearts or CHD. Channelopathies or congenital heart block comprise the diagnoses in those with structurally normal hearts, whereas common diagnoses in CHD include D-TGA, TOF, congenitally corrected transposition, and hypertrophic cardiomyopathy. Patient and procedural risk are often higher in this latter group. The foremost indications for extraction are infection (involving the lead, generator pocket, or valve through which the lead passes), lead dysfunction, or SVC or baffle obstruction. The latter conditions require lead extraction because they are treated by stenting. If a stent were deployed without removing the indwelling leads, the leads would be at risk for entrapment or disruption. This indication is most frequent among patients with d-TGA who underwent the Mustard procedure and now have a systemic venous baffle leak or stenosis (Figure 34.27). Of course, after stenting is performed, new leads are necessary.

Techniques for removal range from the basic to the more advanced. Simple traction or the use of locking stylet may be sufficient in some patients [220]. More specialized equipment is needed in leads that are adherent to venous structures or the myocardium, including mechanical sheaths that break fibrotic attachments, rotational sheaths that pierce adhesions, and electrosurgical dissection sheaths that use RF energy to disrupt attachments [221]. Beyond these interventions are laser sheaths that transmit laser light to facilitate extraction [222, 223].

Awareness of the risks associated with this procedure and strategies to address major complications is essential in developing an anesthetic plan (Table 34.15) [223–225]. Catastrophic vascular or cardiac injury with attempts at lead extraction is a primary concern. This risk increases with (i) years that the leads have been in place, (ii) the number of leads to be explanted, (iii) dual-coil ICD leads (since these are larger), (iv) use of powered sheaths for removal, (v) females with a body mass index (BMI) <25 (presumably due to smaller vessels that may be more prone to injury), and (vi) use of a femoral approach for extraction (a surrogate for a technically difficult procedure) [226–230]. For those patients at increased risk, a surgical team is involved with plans for initiating cardiopulmonary bypass in the event of an otherwise uncontrollable hemorrhage. This can be achieved either through a median sternotomy in patients without prior surgical intervention or through the femoral vessels in patients with a history of sternotomies. Given this possibility, these procedures are most commonly performed in a hybrid CCL.

Anesthetic preparation begins prior to induction by ensuring that any anticoagulation has been held, or if reversal is to be administered if continued. Intraprocedurally, GETA is induced as guided by the patient's clinical condition and cardiac function. Large-bore upper and lower extremity venous access is obtained. The latter is useful in the event of superior vena cava (SVC) or RA tear. If no peripheral access is available in the lower extremity, a 9-Fr introducer sheath is placed in the left femoral vein (leaving the right femoral vein available for emergent bypass cannulation). A dedicated arterial line for blood pressure monitoring is placed (with attention to which extremities may provide the most accurate site in patients with multiple prior cardiac surgeries), and consideration is given to a central venous catheter for the

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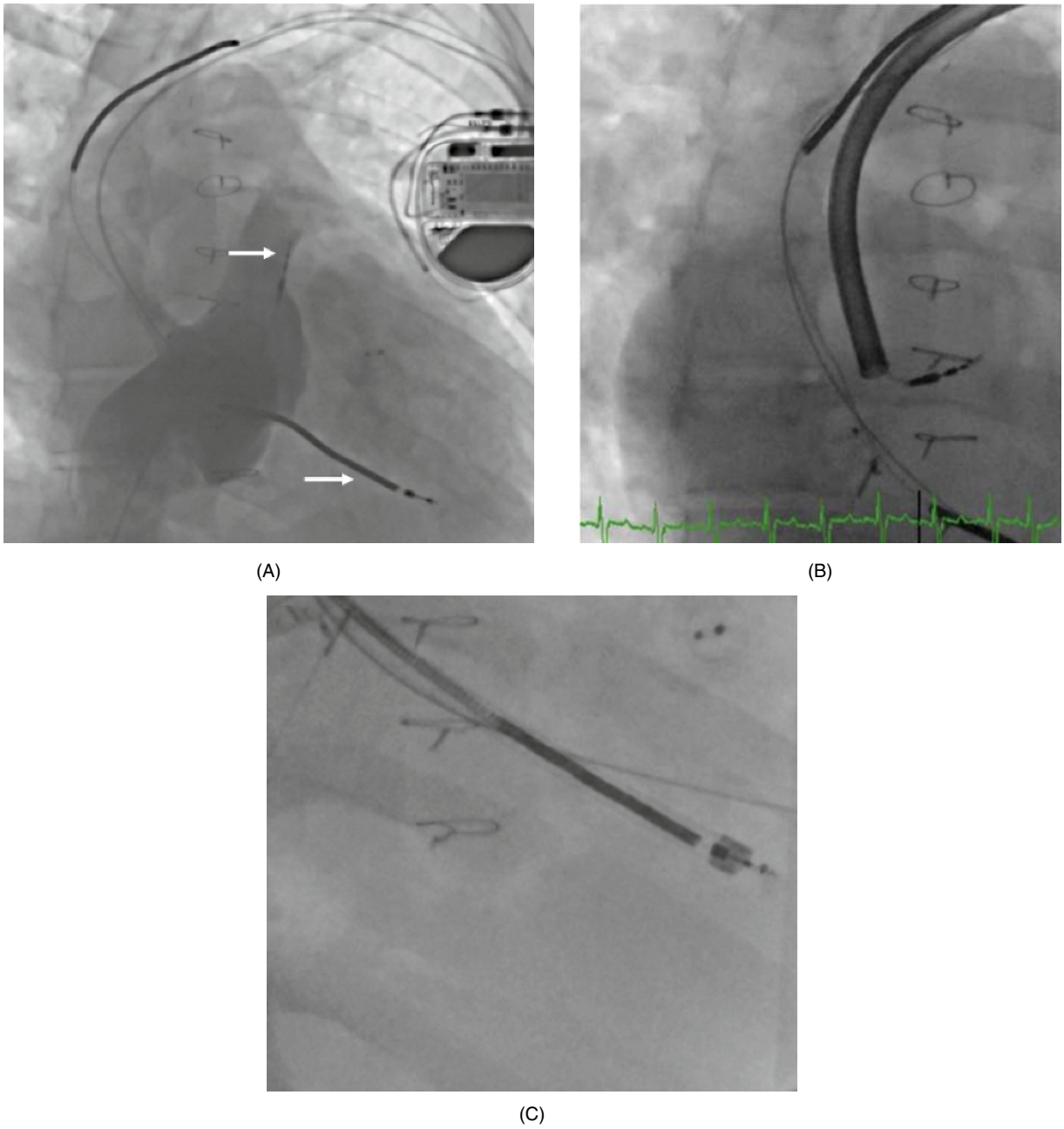


Figure 34.27 Lead extraction. A 33-year-old male with d-TGA status post the Senning procedure and placement of a dual-chamber ICD presented for lead extraction. The leads were 14 years old and were placed for ventricular fibrillation. The ventricular lead was defective and the atrial lead required removal to allow stenting of the baffle stenosis. (A) The atrial baffle of systemic venous blood to the left atrium. Upper arrow marks the atrial lead passing into the left atrial appendage. Lower arrow marks the ventricular lead in the subpulmonic left ventricle. (B) Use of a rotating dilator sheath to extract the atrial lead. (C) Use of a laser device to extract the ventricular lead.

administration of vasoactive agents. Blood, plasma, and vasoactive infusions are ordered and present in the CCL as for a bypass case. In patients who are pacemaker dependent, a temporary pacing catheter is needed in addition to transcutaneous pacing/defibrillation pads. For those undergoing extraction for infection, the development of sepsis should be considered in the differential for hypotension. Imaging of the heart is achieved using a combination of fluoroscopy and echocardiography (intracardiac or transesophageal).

Hemorrhage secondary to venous or cardiac injury is most often temporally related to lead removal. Temporizing measures include administration of volume and pressors while the proceduralist deploys a Bridge Occlusion Balloon™ (Spectranectics) if the source of bleeding is an SVC tear. In the event of hemothorax or pericardial effusion, drains are placed. If needed, the surgical team on standby should be prepared to proceed with cardiopulmonary bypass and sternotomy.

Table 34.15 Management of complications associated with lead extraction

Complications	Management
Hemorrhage	
• Tear at SVC/RA junction	• Passage of a bridging balloon to occlude the tear (performed by the interventionalist) • Administration of volume and vasoactive agents through ***lower extremity*** access • Surgical consult (on standby)
• Cardiac perforation	• Pericardial and/or chest tube drainage and autotransfusion • Surgical consult (on standby)
Hypotension otherwise	
• SVC obstruction by the powered sheath or laser	• Readjust if possible
• Pacing noncapture in those who are pacemaker dependent	• Readjust temporary pacing wire
• Catheter-induced tricuspid valve injury causing severe TR	• Diagnosed via echocardiography. Supportive management with vasoactive agents
• Arrhythmias or decreased contractility associated with tension at the ventricular lead	• Reduce tension applied. Supportive management.
• Blood loss from access site	• Periodically assessed

RA, right atrium; SVC, superior vena cava; TR, tricuspid regurgitation.

Assuming an uneventful extraction, patients are extubated and recovered in the standard anesthesia recovery area. Patients with significant comorbidities, procedural complications, or the continued need for vasoactive agents are monitored postprocedure in the ICU.

Conclusions

The shift from diagnostic to interventional catheterization has resulted in an increase in patient and procedural complexity that has only accelerated in recent years. Such changes have underscored the need for the anesthesiologist to understand each of the ever-expanding variety of procedures that can be performed as well as their associated complications. This added complexity has also highlighted the role that the anesthesia team can play in risk reduction. Through preprocedural communication (with cardiology or the relevant consulting services) and identification of modifiable risk factors, adverse events can be avoided and patient outcomes can be optimized.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

1 Feltes TF, Bacha E, Beekman RH, 3rd, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation 2011;123(22):2607–52. The comprehensive, evidence based document from the American Heart Association laying forth the indications for cardiac catheterization and intervention in congenital heart disease.

32 Twite MD, Friesen RH. The anesthetic management of children with pulmonary hypertension in the cardiac catheterization laboratory. Anesthesiol Clin 2014;32(1):157–73. A now classic, comprehensive review of anesthetic management of the very high risk group of patients with pulmonary hypertension undergoing cardiac catheterization.

44 Hubbard R, Edmonds K, Rydalch E, et al. Anesthetic management of catheter-based patent ductus arteriosus closure in neonates weighing <3kg: a retrospective observational study. Paediatr Anaesth 2020;30(4):506–10. A contemporary case series describing anesthetic management of a newer interventional catheterization procedure: occlusion of the ductus arteriosus in preterm and other small neonates.

46 Odegard KC, Bergersen L, Thiagarajan R, et al. The frequency of cardiac arrests in patients with congenital heart disease undergoing cardiac catheterization. Anesth Analg 2014;118(1):175–82. An excellent review of a single center experience with detailed information about risk factors, resuscitation, and recovery from cardiac arrest in the cardiac catheterization laboratory.

59 Daaboul DG, DiNardo JA, Nasr VG. Anesthesia for high-risk procedures in the catheterization laboratory. Paediatr Anaesth 2019;29(5):491–8. An excellent contemporary review of anesthetic approaches and techniques for interventional and other high risk procedures in the catheterization laboratory.

73 Nasr VG, Callahan R, Wichner Z, et al. Intraluminal pulmonary vein stenosis in children: a "new" lesion. Anesth Analg 2019;129(1):27–40. A recent review of techniques for treatment of pulmonary vein stenosis, and anesthetic considerations for this relatively recent addition to cardiac catheterization lab procedures.

131 Jayaram N, Spertus JA, Kennedy KF, et al. Modeling major adverse outcomes of pediatric and adult patients with congenital heart disease undergoing cardiac catheterization: observations from the NCDR IMPACT registry (National Cardiovascular Data Registry Improving Pediatric and Adult Congenital Treatment). Circulation 2017;136(21):2009–19. A comprehensive effort to model the risk for major adverse outcomes for both adults and children with CHD undergoing cardiac catheterization. Describes the Jayaram Risk Score which is now widely utilized.

132 Lin CH, Desai S, Nicolas R, et al. Sedation and anesthesia in pediatric and congenital cardiac catheterization: a prospective multicenter experience. Pediatr Cardiol 2015;36(7):1363–75. A review of anesthesia related complications in 13,611 pediatric patients at eight centers. The most common reported anesthesia- and sedation-related adverse event was hypotension, occurring in 93 patients (0.68%) primarily with anesthetic induction. Some of these events were associated with CPR and ECMO. High-severity events associated with anesthesia, sedation, and airway management were

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observed in 94 patients (0.69%), with an overall mortality within this group of 0.015%.

145 Odegard KC, Vincent R, Baijal RG, et al. SCAI/CCAS/SPA expert consensus statement for anesthesia and sedation practice: recommendations for patients undergoing diagnostic and therapeutic procedures in the pediatric and congenital cardiac catheterization laboratory. Anesth Analg 2016;123(5):1201–9. A comprehensive, evidence-based, multidisciplinary review and set of recommendations for sedation and anesthesia in the cardiac catheterization laboratory.

223 Bhatia M, Safavi-Naeini P, Razavi M, et al. Anesthetic management of laser lead extraction for cardiovascular implantable electronic devices. Semin Cardiothorac Vasc Anesth 2017;21(4):302–11. A comprehensive review of anesthetic considerations for the high risk procedure of laser lead extraction for implantable cardiac electronic devices.

CHAPTER 35

Anesthesia for Noncardiac Surgery and Magnetic Resonance Imaging

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Introduction

The commonly reported incidence of congenital heart disease (CHD) in the United States is between 4 and 10 per 1,000 live births. The most common defects are ventricular septal defect, atrial septal defect, valvular pulmonary stenosis, tetralogy of Fallot, coarctation of the aorta, atrioventricular (AV) septal defect and transposition of the great arteries. The National Birth Defects Prevention Network data estimate that there are more than 6,100 cases annually of five defects in the US: truncus arteriosus, transposition of the great arteries, tetralogy of Fallot, AV septal defect, and hypoplastic left heart syndrome (HLHS). Annually, there are an estimated 9,200 patients requiring an invasive procedure related to CHD in the first year of life [1].

With improving survival, the number of unrepaired, repaired, and palliated patients of all ages is increasing. With this increase in the number of patients living with CHD, there is a concomitant increase in the number of patients of all ages presenting for noncardiac procedures requiring anesthetic care. Using data from the Pediatric Health Information System (PHIS), an administrative database that includes the surgical data from 52 freestanding children's hospitals, Nasr et al. report a significant increase in noncardiac surgical encounters from 38,272 in 2015 to 45,993 in 2019 ($p < 0.001$) [2]. In fact, also according to PHIS data, 41% of pediatric patients with CHD requiring surgical management of their CHD in the first year of life also have at least one noncardiac procedure before the age of 5 years, most commonly gastrointestinal or otolaryngologic procedures [3]. Adult patients with CHD are also accounting for an increasing percentage of patients presenting for noncardiac surgical procedures and represent a challenge in perioperative management [4].

Data from the Pediatric Perioperative Cardiac Arrest (POCA) Registry report a higher risk of perioperative cardiac arrest in children with CHD undergoing anesthesia compared with the rest of the pediatric population, and 54% of arrests occurred during noncardiac procedures. Mortality after cardiac arrest is also substantially higher for patients with cardiac disease, being 33% among those with heart disease, compared with 23% among those without. It is

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critical to recognize the patients at highest risk of anesthesia-related mortality: infants with single-ventricle lesions and patients with left ventricular outflow tract obstruction (LVOTO), cardiomyopathy or pulmonary hypertension [5, 6]. Risk assessment and stratification has become increasingly important for perioperative planning.

The recognition of high-risk patient groups has led to improved multidisciplinary discussion, selection of appropriate operative venue and recovery area, selection of anesthesia care provider, conduct of anesthesia and surgery, and level of monitoring with the goal of reducing morbidity and mortality. In fact, over the last several years, there has been a reduction in the incidence of mortality in patients undergoing noncardiac surgery at children's hospitals. This is attributed to improved patient selection, medical optimization, and expertise found at dedicated children's hospitals [2].

Over the last several years, the literature suggests that an optimized milieu for the perioperative planning and discussion, acquired and shared expertise in caring for these patients, and multidisciplinary collaboration in care has allowed for improved outcomes in this fragile population undergoing noncardiac procedures. It is possible that shared decision-making allows the group to attempt and be successful in performing procedures on patients that were once deemed too risky.

KEY POINTS: RISKS AND SEQUELAE IN CHD

- There is a higher risk of perioperative morbidity and mortality in patients with CHD.
- Mortality after cardiac arrest is higher for patients with CHD.
- High-risk lesions for anesthesia-related mortality are single ventricle, LVOTO, cardiomyopathy, and pulmonary hypertension.
- Thorough assessment and recognition of high-risk patients leads to improved perioperative planning and optimization of outcomes.

Risk assessment and stratification

Attempts have been made to identify risk factors to help stratify patients with CHD. The pediatric databases of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) classifies patients with CHD according to the residual lesion burden and cardiovascular functional status, dividing them into minor, major, or severe CHD (Table 35.1). Using data from the same database, Faraoni et al. found that children with major and severe CHD undergoing noncardiac procedures have an increased risk of mortality and a higher incidence of postoperative reintubation compared with matched controls undergoing comparable procedures. Interestingly, there was no difference between children with minor CHD and their matched controls [7].

Taking this into consideration, Faraoni et al. identified eight predictors of in-hospital mortality in patients with major and severe CHD and developed a risk stratification score system (Table 35.2). Patients with an overall score of less than or equal to 3 were associated with a low mortality risk (odds ratio [OR]: 1.54, 95% confidence interval [CI]: 0.78–3.04). Those with a score from 4 to 6 had a medium mortality risk (OR: 4.19, 95% CI: 2.56–6.87). Those with a score above 7 had a high mortality risk (OR: 22.15, 95% CI: 15.06–32.59) [8]. A further study by the same group confirmed that the predominant predictors of perioperative mortality in

Table 35.1 ACS NSQIP classification of CHD based on residual lesion burden and functional status

Classification	Definition and criteria
Minor CHD	• Cardiac condition with or without medication and maintenance (e.g., atrial septal defect, small-to-moderate ventricular septal defect with no symptoms) • Repair of congenital heart defect with normal cardiovascular function and no medication
Major CHD	• Repair of congenital heart defect with residual hemodynamic abnormality with or without medications (e.g., tetralogy of Fallot with wide open pulmonary insufficiency, hypoplastic left heart syndrome including stage 1 repair)
Severe CHD	• Uncorrected cyanotic heart disease • Patients with any documented pulmonary hypertension • Patients with ventricular dysfunction requiring medications • Listed for heart transplant

Source: Faraoni et al. [7]. Reproduced with permission of Elsevier.
ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; CHD, congenital heart disease.

Table 35.2 Multivariate risk stratification score to predict postoperative mortality

Variables	B (SE)	OR	95% CI	P	Risk score
Emergency procedure	0.50 (0.17)	1.66	1.19–2.31	0.003	+1
Severe CHD	0.50 (0.19)	1.65	1.15–2.39	0.007	+1
Single ventricle physiology	0.61 (0.26)	1.83	1.10–3.06	0.020	+1
Surgery within 30 days	0.70 (0.18)	2.01	1.40–2.89	<0.001	+1
Inotropic support	0.72 (0.19)	2.05	1.40–3.01	<0.001	+1
Preoperative CPR	0.90 (0.32)	2.46	1.32–4.57	0.004	+2
Acute or chronic kidney injury	1.48 (0.40)	4.42	2.00–9.75	<0.001	+3
Mechanical ventilation	2.05 (0.18)	7.80	5.42–11.21	<0.001	+4

Source: Faraoni et al. [8]. Reproduced with permission of Wolters Kluwer Health, Inc.
Data obtained from multivariable logistic regression and presented as regression coefficient (B), SE, OR, 95% CI. and Wald test *P* value.
CHD, congenital heart disease; CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; SE, standard error.

children with CHD were patient comorbidities and the severity of the cardiac lesion at the time of the noncardiac procedure, not the surgical risk [9].

Preoperative preparation for noncardiac surgery

Multidisciplinary planning

Patients with CHD often have other congenital defects and are often cared for by multiple specialists. Each patient most likely has a pediatrician, a cardiologist, and a cardiac surgeon. The patient may be referred to a general surgeon for a gastrostomy tube placement, a urologist for hypospadias repair, a dentist for dental cleaning and restoration, an orthopedic surgeon for treatment of limb deformities, and multiple other practitioners. In addition, the patient may be scheduled for magnetic resonance imaging (MRI) or computed tomography (CT) scanning to evaluate the cardiovascular system or another co-morbid organ system. Many, if not all, of these procedures require general anesthesia or sedation. The consulted services may not be aware of the patient's anatomy, physiology, and risk associated with anesthesia.

The role of the anesthesiologist in the care of the patient with CHD undergoing noncardiac surgery should not be underestimated. The anesthesiologist may be the member of the collaborative team that understands the most about the surgical procedure, the patient comorbidities, and the anesthetic. A team with ample input from the anesthesiologist should determine where the procedure will take place, such as an outpatient operating room (OR) vs. an OR setup for emergent cardiopulmonary bypass, and how the associated risks can be mitigated. Preoperative management including hydration, medication management, management of anticoagulation, and fasting times should be discussed. In addition, postoperative disposition should be determined in advance, and an intensive care unit (ICU) bed should be reserved if needed.

Multidisciplinary planning can also result in combining multiple procedures under the same anesthetic. The patient may require fewer anesthetics and may be at a lower risk of anesthesia-related morbidity and mortality (see Box 35.1) [10].

Preoperative cardiology visit

The timing of a preoperative cardiology visit prior to a noncardiac procedure depends on the patient's disease, the stage of repair or palliation, and the degree of limitation of activities of daily living (feeding, growing, neurodevelopment for infants; attending school for older children) due to cardiac disease. The type of noncardiac procedure should not impact these guidelines, as a general anesthetic may be required for any procedure. In general, acyanotic patients who are repaired or who have no limitations due to cardiac disease do not require a preoperative cardiology consultation. If these patients have limitations and are not well compensated, a preoperative consultation is indicated within 6 months of the procedure. For patients with cyanotic CHD who are well compensated and have no limitations due to their cardiac disease, a cardiology visit within 12 months of the procedure is adequate. For patients with cyanotic CHD who have limitations due to their cardiac disease, a preoperative consultation is indicated within 6 months of the procedure. Specific recommendations exist for patients with Williams syndrome (see below).

Screening in a pre-anesthetic clinic setting to gather the results of imaging and other diagnostic studies and to review cardiology records is helpful. If necessary, a preoperative cardiology visit can be scheduled, additional tests, studies and consultations can be scheduled, and all data can be collected and reviewed prior to the patient's arrival on the day of surgery. This step facilitates the selection of a properly experienced anesthesiologist as well as the proper setting for the anesthetic, and it allows the anesthesiologist to prepare necessary medications and equipment in advance. A plan for the postoperative recovery site for the patient (post-anesthesia care unit [PACU] vs. ICU) should be made at this time. These preparations translate into fewer cancellations on the day of surgery.

Box 35.1: The advantages of performing multiple procedures under the same anesthetic in patients with congenital heart disease

- Decreased risk of potential anesthetic neurotoxicity (fewer exposures)
- Potential decrease in anesthetic related morbidity and mortality (fewer inductions, intubations, emergences, etc.)
- Less time nil per os
- Less time without cardiac medications such as anticoagulants, diuretics
- Improved patient/parent satisfaction

Interpretation of imaging and hemodynamics

Preoperative imaging and hemodynamic studies are addressed extensively in Chapter 18. Important information obtained from imaging studies and cardiac catheterization include right and left ventricular function, presence of valvular stenosis or regurgitation, the size and direction of flow of atrial and ventricular septal defects, patency of shunts or vascular connections, and an estimate of pulmonary vascular resistance (PVR). These key pieces of information help to identify patients with lesions that place them at an increased risk for perioperative morbidity and mortality (e.g. cardiomyopathy, aortic stenosis, pulmonary hypertension) and to construct an anesthetic plan with appropriate hemodynamic goals.

Nil per os

Fasting times of 6 hours for solids or formula, 4 hours for breast milk, and 2 hours for clear liquids are the recommended guidelines from the American Society of Anesthesiologists.[11]. For patients with CHD, these fasting times are recommended as well. However, there are some important considerations in this patient population. Patients with LVOTO including hypertrophic obstructive cardiomyopathy, subaortic stenosis, aortic stenosis, and supravalvular aortic stenosis (Williams syndrome or non-Williams syndrome); systemic-to-pulmonary artery shunts (e.g. modified Blalock–Taussig shunt, ductal stent, central shunt); and polycythemic, cyanotic patients have an

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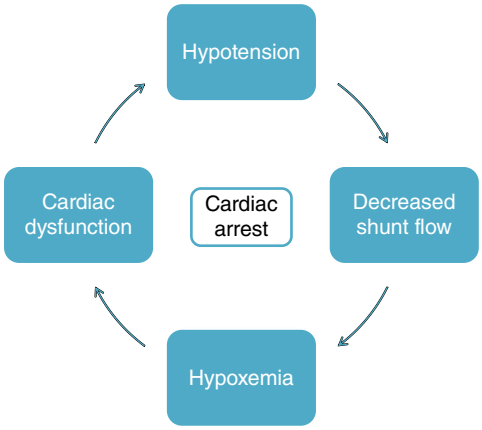


Figure 35.1 The cycle of hypotension and hypoxemia resulting in cardiac arrest in shunted single-ventricle patients.

increased risk of perioperative morbidity and mortality when hypovolemic. Hypovolemic patients with LVOTO may develop significant hypotension during an inhalation induction with a resultant decrease in coronary perfusion pressure that results in unresuscitatable cardiac arrest. Shunted patients with pulmonary blood flow that is completely dependent on systemic blood pressure may become profoundly hypotensive and hypoxemic on induction of anesthesia. Also, when there is decreased blood flow through the shunt, the likelihood of shunt thrombosis increases, as does an unfortunate cycle of hypotension and hypoxemia (Figure 35.1). Other polycythemic, cyanotic patients are at risk for thrombosis and stroke due to increased blood viscosity, which can be due to prolonged fasting. Hypovolemia due to fasting has been reported as a cause of periprocedural morbidity and mortality [12, 13].

Prevention of hypovolemia is the key to minimizing this risk. Careful planning and communication will minimize the time these patients are without fluids. Families should be advised to give clear fluids liberally until 2 hours prior to the procedure, and if the procedure is delayed, clear fluids can be administered by mouth at the hospital until 2 hours prior to the procedure. In addition, intravenous fluids can be started upon arrival in the hospital to replace losses before induction of anesthesia. Patients may also be admitted the night before surgery to receive intravenous fluids while fasting. These strategies may decrease perioperative risk.

Implementation of more liberal guidelines such as allowing clear fluids until one hour prior to the procedure have been shown to be associated with similar aspiration risks as classic NPO guidelines. Liberal guidelines for clears have been adopted in Sweden, Australia, and the United Kingdom with no increase in aspiration. The European Society of Anaesthesiology updated its guidelines as well [14–16]. With this in mind, it may be beneficial to allow patients with a higher hemodynamic risk profile to drink clear fluids until one hour prior to induction to maintain intravascular volume [15, 16].

Continuation of medications

In general, all chronic cardiac medications should be continued perioperatively. Anticoagulants such as aspirin, warfarin, and heparin may be discontinued at the preference of the surgical team after discussion of a perioperative plan for stopping, transitioning, and restarting anticoagulation with the cardiology team. Another exception may be diuretic therapy. Continuation of diuretic therapy in a fasting patient may not be indicated. However, perioperatively, after volume administration, diuretic treatment may be warranted. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may also be held preoperatively due to a significant incidence of hypotension on induction of anesthesia in the general population [17, 18]. These agents have also been associated with hypotension and hemodynamic instability on induction in pediatric patients with CHD undergoing noncardiac operations [19].

Endocarditis prophylaxis

CHD is the leading risk factor for infective endocarditis (IE) in children in the developed world. Lesions associated with increased risk of IE in children are cyanotic CHD, left-sided lesions, and endocardial cushion defects. In addition, the relative risk of developing IE is higher in the 6 months following cardiac surgery and in children less than 3 years of age [20]. The goal of IE prophylaxis is to provide appropriate antibiotic coverage for procedures that are associated with bacteremia. The three most common bacteria implicated in CHD-associated IE are *Streptococcus* (including *Streptococcus viridans*), *Enterococcus*, and *Staphylococcus* species [21].

The 2007 American Heart Association (AHA) guidelines for IE prophylaxis reduced the number of patients with CHD whom they recommend receive IE prophylaxis and reduced the number of procedures for which IE prophylaxis is recommended. The patients with CHD for whom IE prophylaxis is recommended are those who have the highest risk of adverse outcome from endocarditis and these are listed in Box 35.2. Prophylaxis is recommended for patients who are within 6 months of complete repair with prosthetic material or a device. After 6 months, endothelialization of the prosthetic material has occurred, and IE prophylaxis is no longer recommended for these patients.

IE prophylaxis is recommended when both patient indications (Box 35.2) and procedure indications occur. For example, IE prophylaxis is recommended for all dental procedures that involve the manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, but only for patients in Box 35.2. It is also recommended for patients in Box 35.2 who undergo invasive procedures of the respiratory tract that involve incision of the respiratory mucosa, such as tonsillectomy and adenoidectomy or bronchoscopy with biopsy. It is not recommended for bronchoscopy that does not involve incision of the

Box 35.2: Cardiac conditions at highest risk of adverse outcome from bacterial endocarditis

- Cardiac valve replaced by, or repaired with, prosthetic material
- Previous infective endocarditis
- Cardiac valve disease in a transplanted heart
- Unrepaired or palliated cyanotic CHD
- Repaired CHD repaired via surgical or catheter-based technique using prosthetic material for the 6 months following the procedure
- Repaired CHD with residual defect adjacent to prosthetic material

Table 35.3 Infective endocarditis prophylaxis for dental procedures in pediatric patients

Route	Drug and dose
Oral	Amoxicillin 50 mg/kg
Oral – penicillin/ ampicillin allergic	Cephalexin 50 mg/kg or clindamycin 20 mg/kg or azithromycin or clarithromycin 15 mg/kg
Intravenous/ intramuscular (IV/IM)	Ampicillin 50 mg/kg or cefazolin 50 mg/kg or ceftriaxone 50 mg/kg
IV/IM – penicillin/ ampicillin allergic	Cefazolin 50 mg/kg or ceftriaxone 50 mg/kg or clindamycin 20 mg/kg

mucosa. The antibiotic regimen should be active against *viridans* group *Streptococcus* (see Table 35.3). Antibiotic prophylaxis solely to prevent IE is not recommended for endoscopic gastrointestinal or genitourinary procedures that do not incise mucosa, that is, uncomplicated endoscopies; if biopsies are taken then IE prophylaxis should be considered. However, if the patient is known to be infected or colonized, they should be treated with an antibiotic that covers *Enterococcus* [22]. IE prophylaxis is also recommended for high-risk adult patients with CHD undergoing similar procedures. It is important to recognize that IE prophylaxis is also recommended for vaginal delivery and hysterectomy and should be considered for tattoos, and body-piercings [23–26].

KEY POINTS: PREOPERATIVE PREPARATION FOR NONCARDIAC SURGERY

- Multidisciplinary discussion and planning are essential for determining the risk/benefit balance for a given procedure and for mitigating perioperative risk.
- Minimize fasting times, especially for patients at increased risk for hypotension and myocardial ischemia during induction of anesthesia.
- Consideration should be given holding certain cardiac medications prior to surgery, e.g., diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Pacemakers and defibrillators

The number of pediatric patients with cardiovascular implantable electronic devices (CIEDs), pacemakers and defibrillators, has increased as technology has advanced [27]. An increasing number of pediatric patients with these devices will likely present for noncardiac as well as cardiac surgery. It is crucial to manage these devices properly to avoid injury, inappropriate shocking, and hemodynamic instability. A more extensive discussion of pacemaker and defibrillator therapy is presented in Chapters 22 and 34.

Preoperatively, it is important to understand the type of device in place, generator location, associated cardiac disease, indications for placement, and the remaining battery life. The underlying cardiac rhythm and degree of pacemaker dependence for cardiac output (none, partial, or complete) are key points of information. This information is best gleaned from a combination of history, physical exam, review of chest radiograph, discussion with or previous note from the cardiologist, and an interrogation of the device in the holding area by a CIED programmer (cardiologist, specialized nurse, or certified company representative from the device manufacturer).

Electromagnetic interference (EMI) in the OR is most commonly caused by monopolar electrocautery. EMI can result in inappropriate triggering or inhibition of pacing, reversion to asynchronous mode, inappropriate shock or anti-tachycardia therapy, and induction of current in the leads, resulting in myocardial damage. Strategies for reducing EMI include the use of bipolar instead of monopolar electrocautery, using short bursts of cutting rather than coagulation current when monopolar is required, and placing the grounding pad for the electrocautery far from the device site.

If EMI is likely during a procedure, the CIED programmer should reprogram the pacemaker to an asynchronous mode with a rate greater than the patient's intrinsic rate. Similarly, the anti-tachycardia function of a defibrillator should be disabled until the risk of EMI is low. It is critical to monitor the patient for a perfusing rhythm with either a plethysmographic or arterial line waveform, as well as electrocardiogram (ECG), after reprogramming. In addition, temporary pacing/defibrillation equipment must be available at all times, and the availability of appropriately sized equipment must be confirmed.

After the procedure when the risk of EMI is low, the device should be interrogated and reprogrammed back to its original baseline settings. It is critical to monitor for a perfusing rhythm and to have pacing/defibrillation equipment present until the device is reprogrammed [28–30].

A magnet can be used in an emergency situation to reprogram a CIED. It is not a substitute for interrogation/reprogramming by a CIED programmer, and it can have unpredictable consequences, particularly with modern multifunction pacemaker/defibrillator devices. For pacemakers, application of the magnet will usually change the pacemaker mode to an asynchronous mode (AOO, VOO or DOO – see Chapter 22) at a fixed rate, usually between 65 and 100 beats/minute (bpm). This fixed rate is device-specific and dependent on remaining battery life [31]. Untoward effects of magnet application include pacing at a rate or in a rhythm that does not meet the patient's metabolic or hemodynamic needs. For defibrillators, application of the magnet usually suspends the anti-tachycardia function, but does not change the pacemaker to an asynchronous mode. If the patient experiences ventricular tachycardia or ventricular fibrillation while the magnet is applied, the magnet should be quickly removed so that the anti-tachycardia function is restored and the device can deliver a shock [29]. This restoration does not occur with all systems, however; some are disabled until interrogation/reprogramming occurs [32]. There is no substitute for consultation with an expert, assessing the function of the device and converting the functions to an appropriate intraoperative mode. Obviously, there may be emergency situations where this will not be possible. The critical importance of monitoring the patient for a perfusing rhythm throughout

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the procedure, having backup pacing/defibrillation equipment present, and interrogating and reprogramming the device postoperatively cannot be overemphasized. There is a discussion of MRI-compatible pacemakers later in the chapter.

KEY POINTS: PACEMAKERS AND DEFIBRILLATORS

- Preoperatively, all CIEDs should be interrogated and potentially reprogrammed by the CIED service.
- After reprogramming, the patient must be monitored for a perfusing rhythm with an arterial line or plethysmographic waveform.
- Magnet application can have unpredictable consequences and should not be used as a substitute for interrogation and reprogramming.

The patient on ventricular assist device support

Heart failure most commonly resulting from CHD, cardiomyopathy, and myocarditis is the diagnosis associated with more than 12,000 annual pediatric hospital admissions in the United States [33]. Most of these patients can be managed medically or surgically, but there are a growing number of pediatric patients that require extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) placement. There are now devices that are appropriate for all sizes of pediatric patients for long-term support (see Table 35.4) [34, 35]. These devices are discussed in detail in Chapter 37.

After placement, cardiac output can be maintained for these patients until cardiac function recovers or a suitable organ becomes available for transplant. In some cases, the patient can remain on VAD support indefinitely, as destination therapy. Destination therapy has been described in patients with end-stage heart disease due to muscular dystrophy [36]. These patients on long-term VAD support will likely require anesthesia or sedation for multiple imaging procedures and noncardiac interventions and procedures. In order to provide care for this population of patients, one should become familiar with the different types of devices and the management of hypotension, hypertension, and a decrease in output. A perfusionist or VAD-trained nurse should be present for all noncardiac procedures to assist with management and transport of the device. In addition, bacterial endocarditis prophylaxis is warranted in all VAD-supported patients.

The Berlin EXCOR (EXCOR Pediatric Ventricular Assist Device, Berlin Heart, GmbH, The Woodlands, Texas, USA) is a pneumatically driven pump that generates a pulsatile pressure with a rate between 30 and 150 bpm depending on the size of the pump chamber and the size and needs of the patient. The transparent pump chamber allows for visual evaluation of filling, emptying, and thrombus formation. Because of the range of pump sizes, it can be used in neonates, infants, and children, and it is the device that is used most commonly for long-term support in pediatric patients at the present time [35].

Anesthetic management of the patients with a Berlin EXCOR device requires familiarity with the pump and how to troubleshoot hypotension, hypertension, and reduced output. Cave et al. describe a 69% incidence of hypotension in a case series of 29 noncardiac procedures on 11 patients with a Berlin EXCOR device. This group found that hypotension on induction was most associated with the use of remifentanil and was least associated with the use of ketamine as an induction agent. Care should be taken with the administration of anesthetic agents associated with a decrease in systemic vascular resistance (SVR), and intravascular volume and vasoactive agents that increase SVR should be on hand [37].

When caring for a patient with a Berlin EXCOR device, it is critical to maintain the ability to visually inspect the pump. This may require clear drapes, a mirror, and a flashlight. The membrane should be inspected regularly to check for fibrin deposition and for membrane wrinkling. Membrane wrinkling is a sign of incomplete filling of the chamber. Device inspection is a key component of determining the cause of hypotension and the appropriate treatment [34].

Intraoperative emergencies in a patient with a Berlin EXCOR include malignant dysrhythmias, sudden loss of cardiac output, the appearance of air or clot in the pump chamber, and sudden cyanosis. If the patient develops a dysrhythmia, the pump should be examined for filling and output. The right ventricle (RV) can act like a conduit in the short term, and VAD output can be maintained. The patient may require external cardioversion. Loss of cardiac output is most commonly associated with an alarm from the Berlin EXCOR driver unit. It is most commonly caused by a kink in the external tubing of the device. The device should be examined and the tubing unkinked. Appearance of air or clot in the pump chamber can signal an impending embolism.

Table 35.4 Long-term ventricular assist device options for pediatric patients

Device	Positioning	Flow type	BSA (m^2)	Ambulation	Discharge home
Berlin EXCOR®	Paracorporeal	Pulsatile	0.2–1.3	Yes	No
Thoratec®	Paracorporeal	Pulsatile	>0.7	Yes	Yes
Heart Mate II®	Intracorporeal	Axial	>1.4	Yes	Yes
HeartWare®	Intracorporeal	Axial	>0.7	Yes	Yes

Source: Data from Mossad et al. [34].
BSA, body surface area.

A cardiac surgeon and a perfusionist should be called to the bedside for an urgent pump exchange. Sudden cyanosis in a patient with a Berlin EXCOR device may be a sign of pulmonary embolism with right-to-left shunting through an interatrial communication. Transthoracic echocardiography can aid in diagnosis [38].

Most left ventricular assist devices (LVADs) are preload dependent and afterload sensitive. Preload dependence means that, in the case of an LVAD, the left side of the heart must receive enough blood to fill the pump. Lack of left ventricular filling can be due to hypovolemia or right ventricular dysfunction. Treatment can include volume administration and support of the RV either with the administration of inotropic agents or decreasing PVR. Increased afterload can lead to inadequate ejection in the Berlin EXCOR or a decrease in VAD flow in a continuous flow device. The troubleshooting of the Berlin EXCOR and continuous flow devices can be found in Figures 35.2 and 35.3, respectively [39, 40]. In the patient with a right ventricular assist device, the afterload is the PVR which must be managed to facilitate flow.

VAD use in the failed single ventricle population is increasing, although it is fairly uncommon [41, 42]. In the case of the Fontan, there is no "right heart" that must be supported. In this case, preload is maintained through volume administration and the reduction of PVR using standard measures and pulmonary vasodilators such as nitric oxide or sildenafil.

Preoperative evaluation for the patient with a VAD starts with an investigation into the patient's anatomy and indications for VAD placement. An understanding of renal, hepatic, neurologic function should be sought. The patient may be on a variety of medications including diuretics, ACE inhibitors (or other afterload reducing agents), antiarrhythmics, pulmonary vasodilators, and inotropic agents for right heart dysfunction. The patient will also likely be on antiplatelet agents and anticoagulants. The ECG should be reviewed and the rhythm noted. Many patients on VAD

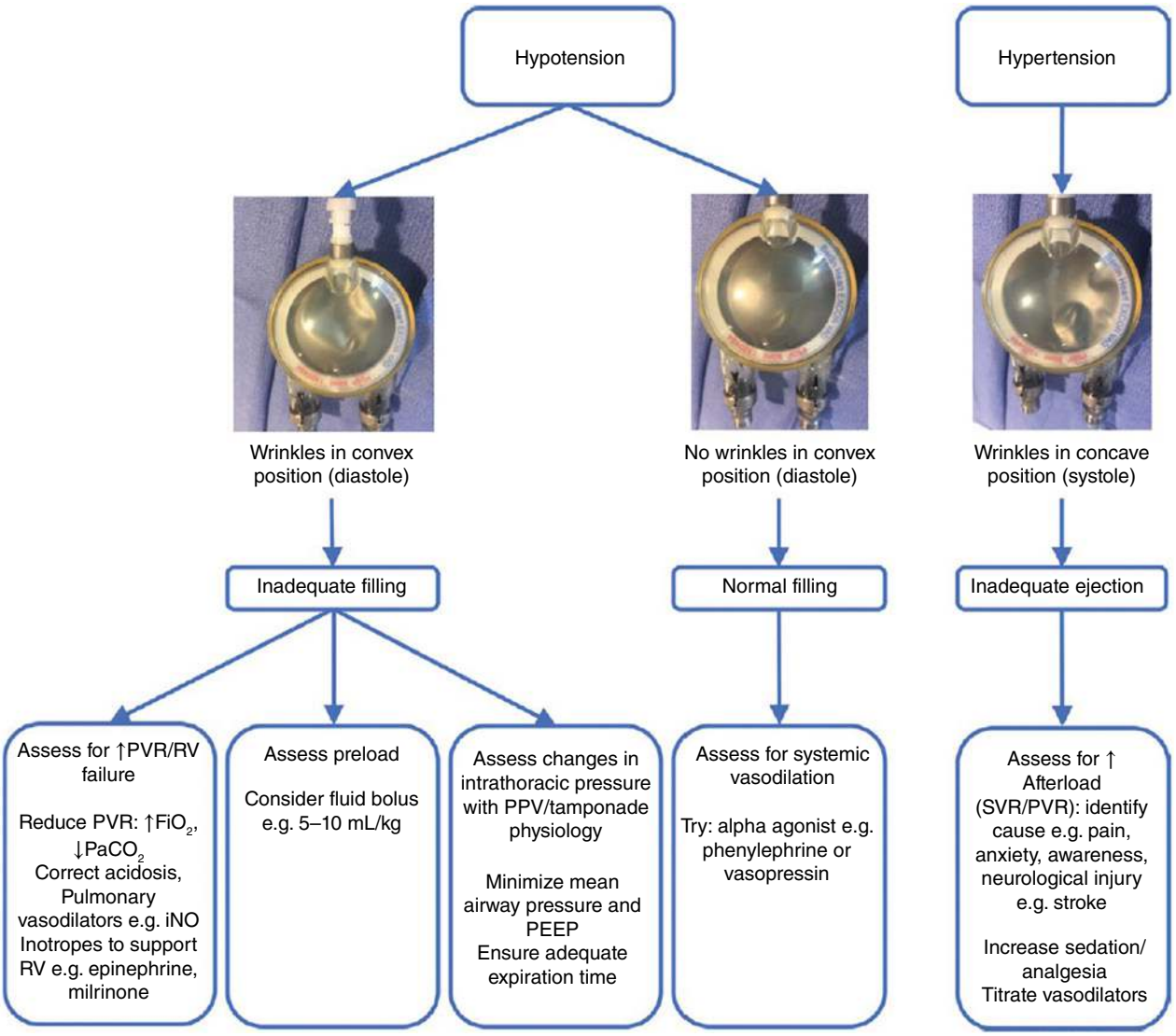


Figure 35.2 Berlin Heart Excor perioperative troubleshooting guide. Target MAPs and flows specific to the patient should be defined preoperatively. iNO, inhaled nitric oxide; PEEP, positive end expiratory pressure; PPV, positive pressure ventilation; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance. (Source: Navaratnam et al. [40]. Reproduced with permission of John Wiley & Sons.)

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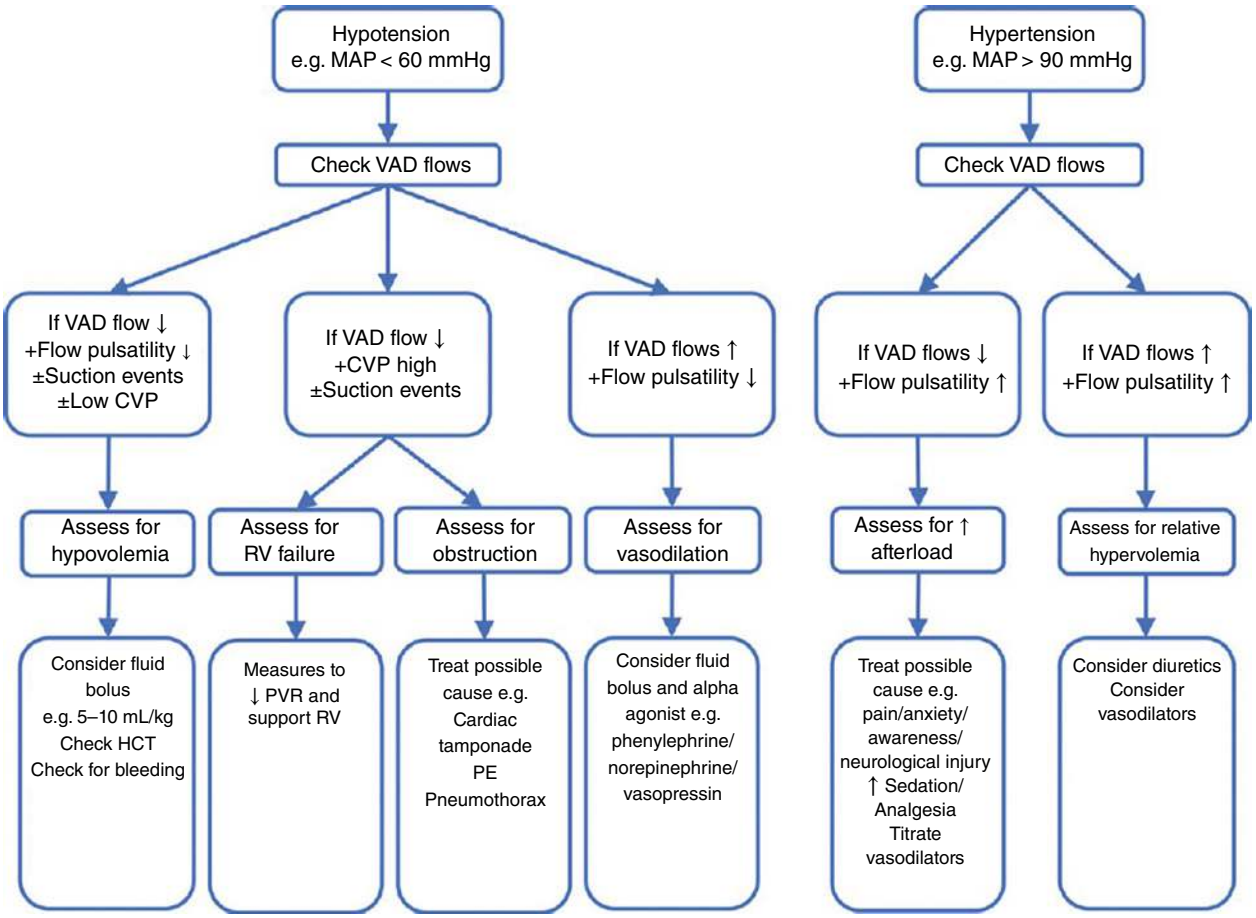


Figure 35.3 Continuous flow devices perioperative troubleshooting guide. Target MAPs and flows specific to the patient should be defined preoperatively. CVP, central venous pressure; LV, left ventricle; MAP, mean arterial pressures; PE, pulmonary embolus; PVR, pulmonary vascular resistance; RPM, revolutions per minute (VAD speed); RV, right ventricle. Source: Navaratnam et al. [40]. Reproduced with permission of John Wiley & Sons.)

support have CIEDs, which should be managed similarly to other patients in the perioperative period. The cardiologist managing the VAD should be contacted, and the VAD should be interrogated for alarm history including low flow, power elevations, malfunction, and backup battery. A recent echocardiogram should also be reviewed. Information about RV function, PVR, and aortic insufficiency should be sought out [39, 40, 43].

Monitoring should include standard ASA monitors: ECG, temperature, capnography, blood pressure monitoring, and pulse oximetry. Unfortunately, with continuous flow devices, pulse oximetry and noninvasive blood pressure (NIBP) monitoring can be unreliable. Invasive arterial blood pressure monitoring should be considered for all cases and is necessary for major noncardiac operations. NIRS monitoring can also yield important information about perfusion and cardiac output. Intraoperative transesophageal echocardiography can be used to optimize right heart function and filling [39, 40, 43].

Intraoperatively, the VAD console for a continuous flow device should be in plain sight and monitored. For the Berlin EXCOR, the chamber should be visually inspected to look for thrombus or membrane wrinkles. The management of systemic vascular resistance is critical for optimal VAD functioning. An age-appropriate MAP should be selected, and optimization of the MAP may include the manipulation of anesthetic depth and the administration of vasopressors and vasodilators. For teenagers and adults, a MAP of 70–80 mmHg should be adequate to maintain good VAD flow and provide an adequate perfusion pressure to end organs. In adults, a MAP greater than 90 mmHg has been shown to be associated with low VAD flow, pump stasis, and embolic stroke [40, 43]. Right heart function may require augmentation with inotropic agents, and PVR may be manipulated to optimize cardiac output.

Data from an adult cohort of 246 VAD patients undergoing 702 noncardiac procedures provide some useful information about perioperative complications and monitoring. The most common perioperative complications were intraoperative hypotension (27%) and acute kidney injury (18%). Interestingly, invasive arterial blood pressure monitoring was only used in 20% of the cases. There were also gaps in blood pressure monitoring of greater than 20 minutes in 55% of cases. There were no recorded blood pressures in 5.5% of cases. During these gaps in monitoring, there is potential for unrecognized hypotension [44].

Postoperatively, the patient should be monitored in a special care or ICU to monitor cardiac, respiratory, and neurologic status. Increases in $PaCO_2$ associated with hypoventilation can lead to increases in PVR and suboptimal filling of the pump, as can hypovolemia associated with fluid shifts. Pain can increase both PVR and SVR and should be managed carefully.

Patients with VAD support may need to undergo noncardiac surgeries where the intraoperative management for the procedure is not aligned with optimal VAD management. For example, during one-lung ventilation for a video-assisted thoracic surgery (VATS), the patient may become hypercarbic and hypoxemia resulting in an increase in PVR, a decrease in right ventricular function, and a decrease device filling. The anesthesiologist should be prepared to take steps to decrease PVR and augment right ventricular function. Transesophageal echocardiography assessing septal configuration, and central venous pressure (CVP) monitoring can facilitate the diagnosis and treatment [45]. Likewise, during neurosurgical procedures, it is important to balance the provision of brain relaxation with the goals for optimal VAD function. In a report of an adult patient undergoing craniotomy for tumor resection, some of the management goals were similar such as the maintenance of a MAP of 70–80 mmHg and hyperventilation. However, mannitol was held due to the effect on preload and the potential for suboptimal VAD function [46].

Of note, the AHA has issued a new statement on resuscitation for the patient with a ventricular assist device. Defibrillation and medication administration per Pediatric Advanced Life Support or Adult Cardiac Life Support Algorithms are indicated, and at this time, external compressions are advised [39, 47]. See Chapter 25 for an extensive discussion of management of cardiac arrest in patients on mechanical support.

KEY POINTS: PATIENTS ON VAD SUPPORT

- Practitioners should become familiar with the common long-term VADs available for pediatric patients.
- Visual pump chamber inspection is critical for the perioperative management of the patient with a Berlin EXCOR device.
- Right heart failure should be considered when LVAD output decreases.

Management strategies for the stages of single-ventricle palliation

The single-ventricle surgical palliation pathway is presented in detail in Chapter 30. An understanding of the anatomy and physiology and familiarity with basic hemodynamic and ventilatory management strategies for the different stages of single-ventricle palliation are important for the successful care of these patients in the noncardiac OR and radiology suite (see Table 35.5). Instability should be anticipated at any stage of single-ventricle palliation, and vasopressors, inotropes, defibrillation capability, and volume expanders should be readily available. In addition, these patients are frequently cyanotic and thus are dependent upon chronically increased red cell mass for oxygen delivery to tissues; packed red blood cells should be available (type and screen or type and cross-match) to transfuse for most surgical procedures. A hematocrit of 40–45% is recommended for cyanotic and shunt-dependent neonates and infants to maintain oxygen-carrying capacity. The superior cavopulmonary anastomosis or Glenn stage of single-ventricle palliation is generally associated with more

Table 35.5 Anesthetic considerations for stages of single ventricle palliation

Stage of palliation	Cardiac lesion	Surgical palliation	Pathophysiological considerations	Anesthetic considerations after palliation
Neonatal	Hypoplastic left heart syndrome	Norwood stage I palliation	Systemic and pulmonary output both ejected by functional single ventricle; pulmonary to systemic vascular resistance ratio determines cardiac output	Avoid hyperoxygenation and hyperventilation; maintain ventricular function; maintain systemic oxygen saturation 80–90%
Neonatal	Tricuspid atresia with no pulmonary stenosis	Pulmonary artery banding, systemic-topulmonary artery shunt, or no intervention	For shunted patients, see above; management of pulmonary to systemic vascular resistance not as critical in banded patients	Maintain ventricular function; maintain systemic oxygen saturation 80–90%
Infant: cavopulmonary connection	Any single ventricle lesion	Superior cavopulmonary connection (bi-directional Glenn operation)	Cerebral-pulmonary-cardiac circulation is predominant in younger infants	Avoid hyperventilation; most stable stage for elective noncardiac surgery
Fontan completion	Any single ventricle lesion	Total cavopulmonary connection (Fontan operation)	Positive pressure ventilation decreases venous return and cardiac output; intolerant of hypovolemia or non-sinus rhythm	Minimize positive pressure ventilation; maintain ventricular volume, sinus rhythm, myocardial contractility; perform elective noncardiac surgery before this stage when possible

Source: Gottlieb and Andropoulos [10]. Reproduced with permission of Wolters Kluwer Health, Inc.

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resilient physiology. The patient is no longer shunt-dependent, the volume burden on the single ventricle is reduced, and cardiac output is not solely dependent on passive pulmonary blood flow as in the Fontan circulation. If possible, elective noncardiac surgery should take place during this stage [10, 48, 49].

KEY POINTS: MANAGEMENT STRATEGIES FOR THE STAGES OF SINGLE-VENTRICLE PALLIATION

- Shunted patients can develop hypotension and myocardial ischemia when hyperoxygenated and/or hyperventilated.
- The Glenn stage of single-ventricle palliation is considered the most stable stage for undergoing elective noncardiac surgery.
- A decrease of cardiac output in the patient with Fontan circulation should be anticipated when initiating positive pressure ventilation.

High-risk patient groups

All the patients included in this section are at increased risk of myocardial ischemia. If the myocardium is poorly perfused and becomes ischemic, an existing low cardiac output state may rapidly progress to an arrhythmia or cardiac arrest. It is the authors' recommendation that care for this population be provided by an anesthesiologist with skill and experience in pediatric cardiovascular anesthesiology. These patients should not receive care in a surgicenter or institution that lacks experts in pediatric cardiovascular intensive care, pediatric cardiology, and pediatric cardiac surgery.

Ductal dependent unpalliated neonates

With advances in care of single ventricle patients, unpalliated, ductal dependent neonates with significant noncardiac comorbidities are presenting for noncardiac surgery prior to addressing the cardiac diagnosis. These procedures can include congenital diaphragmatic hernia repair, tracheoesophageal fistula repair, duodenal atresia repair, exploratory laparotomy for necrotizing enterocolitis, and diverting colostomy for anal atresia. Other procedures related to planning and stabilization of cardiac disease may include peripherally inserted central catheter (PICC) placement, cardiac catheterization procedures, and brain imaging. These procedures can be elective, urgent, or emergent, and any opportunity for multidiscliplinary discussion and planning should be taken. The anesthesiologist should have a detailed understanding of the patient's anatomy and a plan for managing the ratio of pulmonary to systemic blood flow. Central venous and arterial access is advised, and appropriate vasopressors and emergency drugs should be available. ECMO candidacy should be determined preoperatively, and the family should understand the risk associated with both the cardiac disease and the proposed procedure.

CHD associated with tracheoesophageal fistula/esophageal atresia (TEF/EA) conferred a perioperative mortality of 23% compared with no mortality in patients without CHD in a series of 53 patients reported by Diaz et al. In addition, the risk of perioperative mortality was increased in ductal-dependent patients [50]. Also, in a series of 18 unpalliated neonates who underwent emergent general surgical procedures for necrotizing enterocolitis, intestinal atresia, imperforate anus, or tracheoesophageal fistula, 17/18 patients survived to cardiac surgery or palliation. The patient that did not survive to cardiac surgery had a preoperative echocardiographic misdiagnosis and succumbed 3 days after tracheoesophageal fistula repair. All of the ductal dependent neonates survived to operation [51].

Managing these cases can be difficult in the setting of postnatal changes in PVR coupled with one lung ventilation that can be required for tracheoesophageal fistula repair, making the balancing of $Q_p : Q_s$ challenging. Arterial blood pressure monitoring, pre- and postductal oxygen saturation monitoring, frequent blood gas assessment, and cerebral and somatic NIRS monitoring are helpful in this scenario.

Shunt-dependent single-ventricle patients

These patients have a systemic-to-pulmonary arterial shunt that creates a volume burden on their single ventricle from the parallel pulmonary and systemic circulations. They have a reduced oxygen-carrying capacity, and their normal oxygen saturation is 75–85%. They also have reduced diastolic pressure from the run-off of blood into the low-resistance pulmonary circulation through the systemic arterial to pulmonary artery shunt. Instead of a systemic-to-pulmonary artery shunt, many shunted single-ventricle infants will have a right (systemic) ventricle-to-pulmonary artery shunt (Sano shunt). Although theoretically more stable because diastolic blood pressure is usually higher, similar pathophysiological considerations apply, and there are insufficient data reporting outcomes of noncardiac procedures to determine that this shunt lowers the risk of anesthesia. The approach should be the same for all shunted single-ventricle infants before the bidirectional cavopulmonary connection.

This physiologic combination leaves patients particularly vulnerable to hemodynamic insults, and a mild reduction in blood pressure may produce myocardial ischemia. Up to 16% of patients with HLHS who survive the Norwood procedure and are discharged home die prior to their second stage of palliation, which is a reflection of their fragile circulation [52]. These patients frequently have feeding difficulties, and a number of them will undergo gastrostomy tube placement. Slater et al. described good outcomes among 12 patients with HLHS (9 after stage 1 reconstruction, three after stage 2) [53]. At our institutions, even minor noncardiac procedures on shunted single-ventricle patients are performed in the cardiac ORs, and the patients are admitted to the cardiovascular ICU for postoperative care and monitoring.

The hemodynamic condition is optimized by avoiding myocardial depressants and vasodilators. Diastolic hypotension may develop from the use of high inspired oxygen concentration or hyperventilation due to a reduction in PVR. The anesthesiologist should attempt to maintain the oxygen saturation near the patient's baseline. This is accomplished

primarily through the adjustment of minute ventilation. The inspired oxygen concentration is usually maintained close to room air. In addition, hematocrit should be maintained at approximately 45% to maximize oxygen-carrying capacity.

Palliated single-ventricle patients with atrioventricular valve regurgitation

After the second and third stages of single-ventricle palliation (Glenn and Fontan), the vast majority of patients have good cardiac reserve. The volume burden on the ventricle is greatly reduced during the second stage of palliation, and despite remaining cyanotic, myocardial performance improves. Trivial to mild AV valve regurgitation is observed by echocardiography in essentially all single-ventricle patients. However, patients with moderate to severe AV valve regurgitation commonly have a dilated valve annulus and reduced cardiac output. AV valve regurgitation reduces the forward flow of blood and causes the heart to dilate. In this situation, the hemodynamic status is optimized by reducing afterload and maintaining a normal or slightly increased heart rate. Typically, the myocardial depressant effects of even low doses of inhalation anesthetics are poorly tolerated.

Pulmonary hypertension with systemic or supra-systemic PA pressure

This condition is a well-recognized risk factor for perioperative morbidity and mortality. Recent publications report a significantly higher incidence of intraoperative cardiac arrest and death among patients with supra-systemic PA pressures. In a report of 101,500 pediatric anesthetics, of the 10 patients at the Royal Children's Hospital in Melbourne whose death was related to anesthetic management, 50% had pulmonary hypertension [6, 54]. Pulmonary hypertensive crisis is defined by a sudden increase in PVR that results in the PA pressure exceeding mean arterial pressure. This will compromise systemic cardiac output because reduced right ventricular output decreases left heart filling, and RV dilation shifts the interventricular septum leftward, which further impedes LV filling and ejection. Lower blood pressure with increased myocardial oxygen demands leads to right ventricular ischemia. Cardiac arrest rapidly follows [55] (see Figure 35.4).

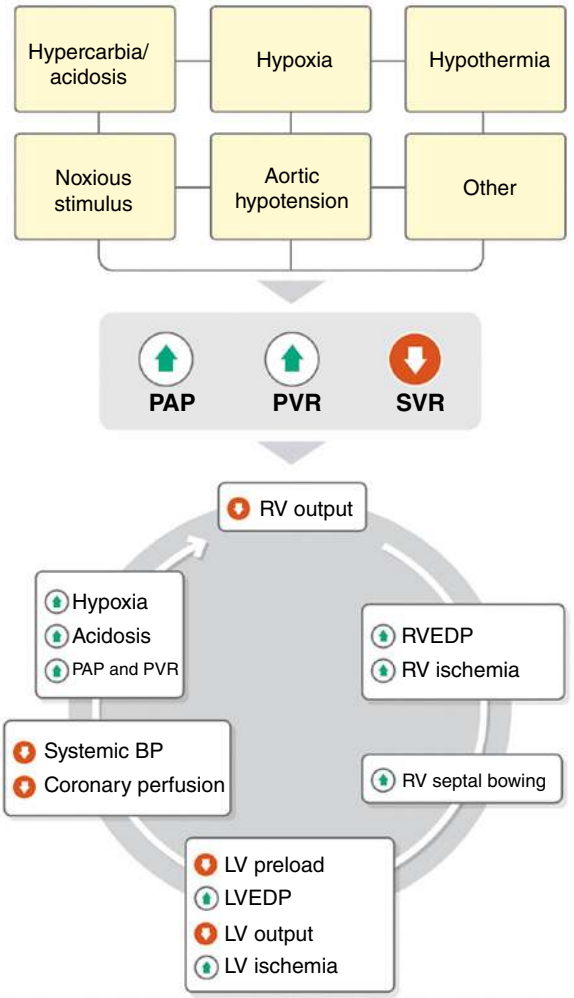


Figure 35.4 The cycle of pulmonary hypertensive crisis. Examples of "other": hypovolemia, anesthesia-induced myocardial suppression, arrhythmias, pneumothorax, pulmonary embolism, sepsis, pericardial effusion, bronchospasm, anaphylaxis, ventilation-perfusion mismatch. BP, blood pressure; LV, left ventricle; LVEDP, left ventricular end diastolic pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RV, right ventricle; RVEDP, right ventricular end diastolic pressure; SVR, systemic vascular resistance. (Source: Latham and Yung [55]. Reproduced with permission of John Wiley & Sons.)

First-line treatment includes increasing the inspired oxygen concentration to 100%, reducing $PaCO_2$, increasing the pH (alkalinization), and initiating inhaled nitric oxide. Hypotension should be treated with phenylephrine or vasopressin to increase coronary perfusion pressure. Epinephrine may also be given to improve cardiac output. Overly aggressive manual ventilation should be avoided because the increase in intrathoracic pressure may reduce venous return, therefore further compromising cardiac filling. The pulmonary vasculature is responsive to changes in pH, and alkalinization with sodium bicarbonate or tromethamine (THAM) can be effective in reducing pulmonary pressures. Some authorities recommend prophylactic preanesthetic administration of inhaled nitric oxide for high-risk patients with pulmonary hypertension [55, 56].

With the widespread use of inhaled pulmonary vasodilators, the use of inhaled iloprost or epoprostenol in the OR as rescue agents has become possible. In order to use either of these medications, a nebulizer can be placed in the anesthesia circuit. When caring for a patient with systemic or suprasystemic PH, the need for this type of rescue should be anticipated and the equipment and drug ordered. Iloprost can be dosed intermittently and carries a risk of bronchospasm [57], while epoprostenol requires continuous delivery and may cause clogging of the circuit filter due to accumulation of the glycine diluent.

It should also be recognized that the perioperative risk of these patients extends into the post-anesthesia recovery period. These patients must be closely monitored, and conditions that increase PVR should be avoided, including hypoxemia, hypercarbia, pain, agitation, and acidosis [56]. Chau et al. provide an excellent discussion of the

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postoperative issues of this high-risk population and a strategy for mitigating the risk postoperatively [58]. See Chapter 33 for a complete discussion of pulmonary hypertension.

Severe aortic stenosis (peak gradient >60 mmHg)

The pressure burden from aortic stenosis causes the ventricle to hypertrophy, but not dilate. Therefore, ventricular function is generally well maintained even with a significant degree of stenosis. These children usually have normal exercise tolerance and appear normal to their families. However, the hypertrophied ventricle is at risk for developing ischemia if the patient becomes hypotensive. If the diastolic blood pressure decreases, as it commonly does during a routine inhaled induction, the ventricle may become ischemic. Bradycardia and/or ST-segment changes may be evident on the ECG. If myocardial ischemia progresses to cardiac arrest, closed cardiac compressions are generally ineffective because of the aortic valve stenosis. As these patients may be sensitive to hypotension, an α-agonist such as phenylephrine must be immediately available and used early if diastolic blood pressure decreases or myocardial ischemia is suspected from a change in the ECG.

Care should be taken to avoid hypotension on induction of anesthesia for these patients. Hypovolemia can lead to an exaggerated decrease in blood pressure with induction. Thus, excessive fasting times should be avoided. Clear liquids should be given up until 1–2 hours prior to the procedure. Intravenous fluids may be started the night before or upon arrival to the day surgery unit to maintain euvolemia. A careful intravenous induction may be preferred for these patients. Medications can be titrated gradually to avoid a decrease in blood pressure, and α-agonists can be administered during induction as needed. Monitoring with an arterial catheter placed prior to induction or soon thereafter may be helpful. Chapter 27 presents a thorough discussion of this lesion and other forms of LVOTO (Williams syndrome, hypertrophic cardiomyopathy; see the following sections).

Williams syndrome

Williams syndrome is cause by a deletion on Chromosome 7q11.3 that codes for the elastin gene and has both cardiac and noncardiac manifestations (see Chapter 8). The most common cardiac manifestations included supravalavar aortic stenosis, pulmonary artery stenosis, and coronary artery abnormalities [59]. In 1996, Bird and colleagues reported a series of ten cases of sudden death in patients with Williams syndrome, many of which were associated with an anesthetics or where the patient had had an intraoperative cardiac event previously [60]. And so began the awareness of the risk associated with anesthesia, the path to understanding, and the push for risk stratification and mitigation in this group of patients.

In 2006, Burch et al. improved the understanding of the anatomic and physiologic basis for sudden death under anesthesia, which is the imbalance between myocardial oxygen supply and demand. In short, myocardial oxygen supply can be decreased due to the loss of diastolic elastic recoil in the aorta which decreases the coronary perfusion pressure during diastole, dysfunctional adherence of the aortic valve leaflets to the sinotubular ridge leading to decrease blood flow in the sinuses of Valsalva, and ostial narrowing of the coronary arteries themselves. Decreases in systemic vascular resistance related to anesthetic agents or relative hypovolemia add to decreased myocardial oxygen supply. Myocardiac oxygen demand is increased by ventricular hypertrophy and increased end-diastolic pressure in one or both ventricles. Tachycardia related to stress, laryngoscopy, or a light plane of anesthesia can also increase myocardial oxygen demand. These patients can also be difficult to impossible to resuscitate [61].

Several publications of institutional experiences have helped to define the incidence of cardiac morbidity or cardiac arrest associated with anesthesia and the patient factors that increase risk. Olsen et al. reviewed 108 anesthetics in 29 patients over a span of 35 years, from 1974 until 2009. The incidence of a cardiac complication including bradycardia, hypotension, hypertension, arrhythmia, ECG changes or cardiac arrest was 11.1%, and the risk of cardiac arrest was 1.85%. Severe outflow tract obstruction, abnormal coronary perfusion, and younger age appeared to be associated with a higher risk of cardiac morbidity or arrest [62]. Latham et al. reviewed the records of 48 patients with elastin arteriopathy (both Williams and nonsyndromic) who underwent 141 anesthetics between 1990 and 2013. Seven patients experienced a cardiac arrest (15% of patients, 5% of anesthetics) and there were nine cardiovascular complications (15% of patients, 6% of anesthetics). Extracorporeal support was required in five cases. The highest risk of cardiac arrest was in children less than 3 years old and with bilateral ventricular outflow tract obstruction (BVOTO) [63]. Last, Brown et al. reviewed the records of 75 patients undergoing 202 anesthetics (both cardiac and noncardiac procedures) from 2012 to 2016. Of the noncardiac procedures, there were no cardiac arrests and 95.7% did not have an adverse cardiovascular event. Of the cardiac procedures, there were two cardiac arrests, one requiring extracorporeal support. There were no cardiovascular adverse events in 85.7% of these cases [64].

Risk assessment in patients with Williams syndrome is challenging. There are certainly factors that place a patient in a higher risk category; however, cardiac arrest can occur even in the absence of risk factors [65]. A risk stratification strategy developed by Matisoff et al. and modified by Collins et al. is presented in Table 35.6 [65, 66]. Of note, evaluation of the ECG for a prolonged corrected QT interval is part of the stratification process. A prolonged QTc is seen in 13% of patients with Williams syndrome and may be related to microischemia from BVOTO or to ventricular ectopy and the risk of sudden death from arrhythmia.

Recommendations for perioperative care of patients with Williams syndrome can be found in Table 35.7 [66]. Of note, for all risk categories (including low risk), the induction should take place in a location that is appropriate for a resuscitation. Vasoactive medications and a defibrillator with appropriately sized pads should be immediately available. Patients with Williams syndrome should be cared for at hospitals with pediatric anesthesiologists, pediatric cardiac anesthesiologists, cardiologists, cardiac surgeons, pediatric cardiac intensivists, and ECMO capability. These patients are

Table 35.6 Risk stratification for anesthetic administration in patients with Williams syndrome

Low risk	Moderate risk	High risk
Age >20 years	Hypertension	Age <3 years
No cardiac involvement greater than mild supravalvar or branch pulmonary artery stenosis	Moderate supravalvar or branch pulmonary artery stenosis	History of adverse cardiovascular event
Normal ECG	Mild bilateral outflow tract obstruction	Preprocedural arrhythmia
No renal artery involvement	Renal artery stenosis	Bilateral outflow tract obstruction of ≥moderate severity
	Renal dysfunction	SVAS gradient of ≥40 mmHg and the presence of left ventricular hypertrophy
	QTc on ECG >450 ms but <500 ms	Coronary artery involvement
	Airway abnormalities, lung disease, or severe gastroesophageal reflux	Diffuse stenosis of the thoracic aorta
		≥Moderate left or right ventricular hypertrophy Symptoms or ECG signs of ischemia
		QTc on ECG ≥500 ms

Source: Collins et al. [65]. Reproduced with permission of John Wiley & Sons.
ECG, electrocardiogram; ms, milliseconds; QTc, corrected QT interval on ECG.

not good candidates for outpatient surgery center or office anesthesia or sedation [65, 66].

Preoperative evaluation should include a cardiologist evaluation within one month of the planned procedure [59, 65]. Patients with Williams syndrome can experience rapid changes in the cardiovascular manifestations of the syndrome. In addition, it should be recognized that an unremarkable previous anesthetic does not guarantee an uneventful future anesthetic. The ECG should be reviewed carefully for signs of ischemia, arrhythmia, and prolonged corrected QT interval. Time without fluids should be minimized. Scheduling the patient for the first case of the day helps to avoid lengthened fasting time due to delays. An intravenous catheter can be placed for hydration, as well, and high-risk patients may be admitted preoperatively for intravenous hydration. Postoperative disposition should be determined preoperatively, and a monitored bed should be secured [59, 65, 66]. Williams Syndrome patients with significant SVAS and coronary involvement should be considered for cardiac surgical intervention first, before any noncardiac procedures, whenever possible.

The hemodynamic goals for the anesthetic include the maintenance of preload and systemic vascular resistance and the avoidance of tachycardia and increased PVR. This can be accomplished with various anesthetic agents, and treatment of hypotension should be swift, usually with phenylephrine or vasopressin. The monitoring of frequent noninvasive (or invasive) blood pressures and a five lead ECG for signs of ischemia are critical. Most impending cardiovascular catastrophes in these patients involve ST segment changes, hypotension, and bradycardia.

Many parents of children with Williams syndrome are aware of the risk of cardiac arrest associated with anesthesia. The anesthetic consent process should involve a discussion of this risk and the preparations that are taking place to mitigate the risk.

Adults with Williams syndrome should be evaluated closely as well. Adults with mild disease are usually not at an increased risk. However, adults who have undergone intervention for severe disease earlier in life may need reoperation and should be evaluated for recurrence of obstruction prior to being anesthetized. Electrocardiographic evidence of ventricular hypertrophy should be investigated. Diabetes mellitus, obesity, and accelerated atherosclerosis are also common comorbidities in patients with Williams syndrome and should be noted during preoperative evaluation [67, 68].

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) makes up 25% of cardiomyopathies in children, and it is the most common cause of sudden cardiac death (SCD) in children. HCM is most commonly due to mutations in the genes encoding the myosin-binding protein C and the beta-myosin heavy chains. Other etiologies include syndromes (Noonan, Costello, and others) [69, 70].

Preoperative evaluation of the echocardiogram should focus on the degree of hypertrophy and the two-dimensional left ventricular mass (2DLVmass) index. Increased 2DLV mass index can help to risk stratify patients with HCM for perioperative events [70]. Other pertinent echocardiography findings may include LVOTO and evidence of diastolic dysfunction due to the increased ventricular wall thickness. A significant decrease in LV mass over time may represent the progression of the cardiomyopathy into end stage heart disease characterized by systolic dysfunction [71]. The patient's risk factors for SCD should also be noted. SCD incidence peaks in the 8- to 16-year-old age range, and many patients have an implantable cardiac defibrillator in place. Myocardial bridging in which heart muscle surrounds a coronary artery has an incidence of 28% in pediatric patients with HCM undergoing cardiac catheterization. This anatomic condition may also predispose to ischemia [72].

It is important to recognize that the lack of LVOTO on an echocardiogram at rest does not mean that LVOTO will not occur perioperatively. In addition, patients with major risk factors for SCD may also represent patients with increased risk of perioperative morbidity (Table 35.8) [73]. Asymptomatic patients may become symptomatic in the perioperative period.

The perioperative management of HCM-associated LVOTO, diastolic dysfunction, potential ischemia, and dysrhythmias represent challenges to the care team. Increases

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Table 35.7 Anesthetic management of (a) low-risk, (b) moderate-risk, and (c) high-risk patients with WS

Preanesthesia planning	Induction and maintenance of anesthesia	Anesthesia emergence and disposition
(a)		
Schedule preanesthesia visit 1–2 weeks prior to planned surgery focusing on airway, development, cardiac, gastrointestinal, renal disease	Minimize npo (nothing by mouth) time and liberalize preoperative oral fluids	Monitor for emergence tachycardia and ECG changes
Continue beta-blockers on day of anesthesia	May need oral premedication prior to induction with midazolam, pentobarbital, ketamine	Aggressively manage postoperative pain and shivering to reduce oxygen consumption
Induce anesthesia in an area suitable for resuscitation (operating room, catheterization lab, ICU)	Use full ASA monitors, including 5-lead ECG	Monitor after anesthesia for at least 2 hours
Have resuscitation drugs, including vasopressors, immediately available	Use slow, titrated mask induction or IV induction with ketamine, etomidate, narcotics, or small doses of propofol Employ balanced anesthetic with drugs that reduce myocardial oxygen consumption and minimize reductions in SVR Treat ST changes with vasopressors	
(b)		
Consider transfer to center with pediatric cardiology and pediatric anesthesia for all nonurgent anesthesia	Minimize npo time and liberalize preoperative oral fluids	Monitor for emergence tachycardia and ECG changes
Schedule preanesthesia visit 1–2 weeks prior to planned surgery, focusing on airway, development, cardiac, gastrointestinal, renal disease	May need oral premedication prior to induction with midazolam, pentobarbital, ketamine	Aggressively manage postoperative pain and shivering to reduce oxygen consumption
Continue beta-blockers on day of anesthesia	Use full ASA monitors, including 5-lead ECG	Recover in high-acuity setting with capability for resuscitation
Induce anesthesia in an area suitable for resuscitation (operating room, catheterization lab, ICU)	Use slow, titrated mask induction or IV induction with ketamine, etomidate, narcotics, or small doses of propofol	Monitor after anesthesia for at least 6 hours, and preferably overnight, prior to discharge
Have resuscitation drugs, including vasopressors, immediately available	Employ balanced anesthetic with drugs that reduce myocardial oxygen consumption and minimize reductions in SVR Treat ST changes with vasopressors	
(c)		
Pediatric or cardiac anesthesia team involved in care should have experience in managing patients with WS	Place IV for prehydration	Monitor for emergence tachycardia and ECG changes
Transfer to facility with ECMO availability	May need oral premedication prior to IV placement, with small doses of midazolam, ketamine, or pentobarbital	Aggressively manage postoperative pain and shivering to reduce oxygen consumption
Continue beta-blockers on day of anesthesia	Use full ASA monitors, including 5-lead ECG	Recover in high-acuity setting with capability for resuscitation and ECMO deployment
Induce anesthesia in an area suitable for resuscitation (operating room, catheterization lab, ICU)	Induce via IV with etomidate, fentanyl, ketamine	Monitor after anesthesia for at least 6 hours, and preferably overnight, prior to discharge
Ensure that ECMO team is aware and clear-primed ECMO circuit is nearby	Employ balanced anesthetic with drugs that reduce myocardial oxygen consumption and minimize reductions in SVR	
Have resuscitation drugs, including vasopressors, immediately available	Consider direct monitoring of myocardial contractility with echocardiogram in more complicated or prolonged cases Treat ST changes with vasopressors Monitor status of resuscitation with echocardiogram to evaluate contractility Deploy ECMO early if standard resuscitation measures are unsuccessful	

Source: Matisoff et al. [66]. Reproduced with permission of John Wiley & Sons.

Table 35.8 Categorical predictors of 5-year sudden cardiac death risk in children with hypertrophic cardiomyopathy

Model	Hazard ratios (95% CI)
Clinical	
Prior history of nonsustained ventricular tachycardia	2.87 (1.00–6.57)
Prior history of syncope	7.40 (1.21–32.81)
Clinical/genetic	
Prior history of nonsustained ventricular tachycardia	2.58 (1.00–6.17)
Prior history of syncope	7.23 (1.09–33.57)
Pathogenic variant in any gene (reference: confirmed absence of variant)	1.32 (1.00–2.12)

Source: Miron et al. [73]. Reproduced with permission of Wolters Kluwer Health, Inc.

Table 35.9 Comorbiditics and indicators of increased mortality in patients with Eisenmenger syndrome or intracardiac shunts with pulmonary hypertension that should be reviewed prior to any surgical procedure

Frequent comorbidities	Indicators of increased mortality
Erythrocytosis	SaO_2 < 85%
Thrombocytopenia	History of syncope
Cerebrovascular Accidents	Younger age at time of symptom onset
Hepatic insufficiency	Younger age at time of symptom onset
Renal insufficiency	Fixed and elevated PVR
Coagulopathy	Atrial arrhythmias
Coronary artery disease	Right heart failure
Endocarditis	Pregnancy
Trisomy 21 Cerebral abscess	NYHA class III-IV

Source: Bennett et al. [81]. Reproduced with permission of Elsevier.
PVR, pulmonary vascular resistance; NYHA, New York Heart Association.

in LVOTO can be minimized by maintaining preload and systemic vascular resistance and by avoiding increases in heart rate and contractility. Hypotension should be treated with vasoconstrictors like phenylephrine or vasopressin, rather than ephedrine or other inotropes that increase contractility and heart rate. Hypertrophy-related diastolic dysfunction confounds intravascular volume management and favors a slower heart rate and sinus rhythm. Hypervolemia may result in pulmonary edema and should be avoided. A slower heart rate and the atrial contraction in sinus rhythm facilitate improved filling and coronary perfusion. The risk of ischemia is increased due to LVOTO, the increased myocardial oxygen demand of a hypertrophied ventricle, and a myocardial oxygen supply that changes with heart rate and thus time spent in diastole, as well as the potential for myocardial bridging. Arrhythmias including bradycardia, atrial fibrillation or supraventricular tachycardia, or ventricular tachycardia or fibrillation should be anticipated. The ECG should be monitored closely, and tachyarrhythmias should be managed expeditiously by medication administration or cardioversion, as indicated. Patients with HCM are difficult to resuscitate in the event of a cardiac arrest and early defibrillation is critical. [70, 71, 74].

Transplant coronary artery disease

The incidence of transplant coronary artery disease (TCAD) (also known as coronary allograft vasculopathy) in pediatric patients is 17% at 5 years after cardiac transplantation, and 24% of patients with any degree of TCAD died within 2 years in a recent report. A multi-institutional study found that the major risk factors for TCAD were older recipient age and donor >30 years of age [75]. Patients who have experienced recurrent rejection, new onset arrhythmias, unexplained recurrent chest or abdominal pain, and/or the development of systolic or diastolic dysfunction should may have TCAD [76]. Symptoms of TCAD are often atypical due to the denervation of the transplanted organ. However, the symptom complex of abdominal, chest, and/or arm pain should raise suspicion [77]. These patients should have routine cardiac catheterization with coronary angiography. Hemodynamic assessment is useful as patients with higher right ventricular end diastolic pressure and capillary wedge pressure have an increased risk of TCAD [76]. The anesthesiologist should consider all heart transplant patients to be at risk, even patients who have had normal coronary angiography in the past. This risk increases with greater time after transplant. Excessive decreases in coronary perfusion pressure should be avoided, the ECG should be carefully monitored for signs of ischemia, and hypotension should be treated early with α-agonists. See Chapter 32 for further discussion of this entity.

Eisenmenger syndrome

Eisenmenger syndrome is fortunately rarely seen in this era. In our institutions, most children who have developed Eisenmenger syndrome have recently emigrated from a country where indigent patients do not have access to pediatric cardiovascular surgery. Like pulmonary hypertension, these patients have a reactive pulmonary vasculature and should be managed similarly.

Eisenmenger syndrome is a complication of uncorrected intracardiac shunt or shunts leading to irreversible pulmonary hypertension and shunt reversal. This leads to cyanosis and polycythemia over time. Due to the right-to-left pop-off through the intracardiac shunt, cardiac output can be preserved. Fortunately, Eisenmenger syndrome has become less common due to the early repair of shunt lesions and the now routine repair of cardiac lesions in patients with trisomy 21 and other syndromes. Chronic treatment with medications such as phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostanoids leads to increased survival in this group of patients, and these patients will need noncardiac procedures during their lives [78].

The perioperative risk of mortality in patients with Eisenmenger syndrome undergoing noncardiac surgery has been reported to be as high as 20–30% [79, 80]. Indicators of increased mortality and common comorbidities are found in Table 35.9 [81]. However, modern data suggest that this fragile patient population is most safely cared for with proper planning and consultation and adherence to hemodynamic goals. Bennett et al. report their institutional experience in caring for

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33 patients with Eisenmenger syndrome/physiology undergoing 53 procedures. The most common adverse event was hypotension (44%). Two patients in the series expired within 30 days of an anesthetic, yielding a mortality risk of 3.8%. Avoidance of hypotension using vasopressors such as phenylephrine and vasopressin is critical, and the authors recommend the administration of a vasopressor prior to or during induction of anesthesia [81]. Prevention and treatment of increases in PVR are also very important. Hypoxia, hypercarbia, acidosis, light anesthesia, pain and agitation all contribute to increases in PVR. These should be avoided if possible, and maneuvers including hyperventilation, increased oxygen administration, and increased depth of anesthesia should be considered. Medications to decrease PVR including inhaled nitric oxide and inhaled or intravenous prostacyclin should be readily available. Postoperative disposition should be planned preoperatively, as the risk of morbidity and mortality continues in the postoperative period [78, 81].

Adult congenital heart disease

The number of adults living with CHD are increasing in Western countries due to advancements in care (see Chapter 20). The number of adult patients with CHD presenting for noncardiac surgery is also increasing. These patients may be unrepaired, repaired, or palliated. Patients may have residual and acquired cardiac disease, and they may have comorbid conditions associated with CHD such as arrhythmia, renal impairment, pulmonary insufficiency, liver dysfunction, coagulopathy, and cognitive disability. They may also have cardiac and noncardiac comorbidities associated with aging including diabetes, coronary artery disease, chronic obstructive pulmonary disease, and obesity [82].

There is a spectrum of disease and follow up for adults with CHD. Many adult patients with CHD consider themselves healthy after repair of their CHD. Low-risk lesions that are repaired early in life, including patent ductus arteriosus (closed before age 2), isolated ASD (corrected before age 12), and isolated VSD (closed before age 2, without residual shunt), may be considered "cured" [23, 24]. These patients may not be followed for their CHD. These may seek care in the community. Most other patients have residual issues linked to their CHD. These patients are followed by ACHD specialists and should be cared for at ACHD centers [24]. Patients with ACHD are usually either followed specialized ACHD centers which are either pediatric hospitals where practitioners are familiar with CHD or adult hospitals with CHD support. Patients with ACHD treated at specialized ACHD centers have been shown to have better outcomes than those who are not [83]. In addition, the impact and severity of ACHD may be minimized at non-ACHD centers due to a lack of familiarity with rare diagnoses, long interval from original cardiac interventions, and an impression that the CHD is "fixed" and no longer an issue [4].

Patients with ACHD have been shown to be at increased risk of perioperative morbidity and mortality when undergoing noncardiac surgery [4, 84]. An increased risk of death was found to be associated with the presence of a VSD, trisomy 21, and pulmonary hypertension [84]. Data from the Closed Claims Database of adults with CHD undergoing noncardiac surgery indicate that the most common factors contributing to adverse events were preoperative assessment and optimizations (40%), CHD (50%), and postoperative monitoring and care. In fact, up to 48% of the adverse outcomes could be attributed to lack of knowledge about CHD [85].

Risk assessment for these patients is complicated, but some guidance exists. The Mossad Risk Assessment Tool is a point system of preprocedural risk stratification of patients with ACHD (Table 35.10) [82]. Patients in the minimal perianesthetic risk group can usually be cared for in an outpatient setting. Patients in the moderate perianesthetic risk category would likely benefit from postprocedural admission and transfer to a specialized ACHD center should be considered. Patients in the high perianesthetic risk category should be admitted to an ICU and be cared for at a specialized ACHD center [23, 24, 82].

Preoperative evaluation should include a detailed investigation into the cardiac diagnosis, all cardiac surgeries and

Table 35.10 Mossad risk stratification uses a point system to assess adult congenital heart disease

	0	1	2
CHD diagnosis	Simple (ASD)	Moderate (ASD + PS)	Severe (ToF)
CHD intervention	Corrected, No residual	Corrected with residual	Palliated
Ventricular obstruction	None	Yes, gradient <49 mmHg	Yes, gradient >50 mmHg
Ventricle, number, and position	2 LV is systemic ventricle	1 LV is systemic ventricle	1 RV is systemic ventricle
Dysfunction systemic ventricle	Mild	Moderate	Severe
PVR	Normal, <2 wood Units	2–4 wood units	>4 wood units
SaO_2	>90%	75–90%	<75%
Hct	30–45%	25–30% or 45–65%	>65%
Arrhythmias	Seldom	Atrial level	Ventricular level
Number of cardiac medications	1	2	≥3

Source: Lei and Heggie [82]. Reproduced with permission of John Wiley & Sons.

Note: Points are added for each line, following which risk is assessed based on the total number of points, as follows: 0–6 points: minimal peri-anesthesia risk (outpatient); 6–13 points: moderate peri-anesthesia risk (possible same day admission); 14–20 points: high peri-anesthesia risk (possible ICU admission). Modified from Mossad E, presented during the Society of Cardiothoracic Surgeons Annual Meeting in 2002.

ACHD, adult congenital heart disease; ASD, atrial septal defect; ICU, intensive care unit; LV, left ventricle; PS, pulmonary stenosis; PVR, pulmonary vascular resistance; RV, right ventricle; S_aO_2, systemic oxygen saturation; ToF, tetralogy of Fallot.

catheterizations, ECG or Holter, and recent imaging (cardiac MRI, CT angiogram, echocardiogram). The patient should be questioned regarding exercise tolerance, palpitations, dizziness or syncope, chest pain, orthopnea, or cyanotic spells [23]. For patients in the high perianesthetic risk category according to the Mossad Risk Assessment Tool, a cardiac catherization prior to the noncardiac procedure may be useful for quantifying $Q_p : Q_s$, evaluating the degree of pulmonary hypertension and reactivity, assessing gradients across valves, performing electrophysiology testing and ablation, and possibly ballooning valvular stenoses or placing percutaneous valves to improve the patient's risk profile [24]. In addition, exercise or pharmacologic stress testing should be considered, as well as coronary angiography or CT coronary angiography, as patients with ACHD may have an anomalous coronary, a coronary artery that has been reimplanted as part of a repair/palliation, and/or acquired atherosclerotic coronary artery disease [86].

The 2018 ACC/AHA Guideline for the Management of Adults with Congenital Heart Disease provides a useful recommended checklist for patients with ACHD preparing for noncardiac surgery (Table 35.11) [87].

It is critical for anesthesiologists to be part of the multidisciplinary team that is planning and coordinating care for patients with ACHD with special consideration of SBE prophylaxis, management of anticoagulation, preoperative management, invasive monitoring and postoperative disposition [88]. It is recommended that the multidisciplinary team meet with the patient in advance. Many patients have significant anxiety related to medical procedures and addressing the perioperative issues and plan well before the procedure can help the patient and the care team [23]. Advanced directives should also be considered and clarified. Intentional multidisciplinary decision-making and planning is critical for the optimization of care for this group of patients that is high risk for perioperative morbidity and mortality.

Table 35.11 ACHD management issues for noncardiac surgery

Clarify CHD diagnosis
- Clarify prior procedures, residua, sequelae, and current status, including ACHD AP classification
- Be aware that history obtained from only the patient and family may be faulty or incomplete
- Obtain and review old records to ensure accurate understanding of past procedures and clinical course
- Complete additional investigations required to define ACHD AP classification
- Develop management strategies to minimize risk and optimize outcome

Factors associated with Increased risk of perioperative morbidity and mortality

(S3.12-12):
- Cyanosis
- Congestive HF
- Poor general health
- Younger age
- Pulmonary hypertension
- Operations on the respiratory and nervous systems
- Complex CHD
- Urgent/emergency procedures

Issues to consider
- Endocarditis prophylaxis
- Complications related to underlying hemodynamics
- Abnormal venous and/or arterial anatomy affecting venous and arterial access
- Persistent shunts
- Valvular disease
- Arrhythmias, including bradyarrhythmias
- Erythrocytosis
- Pulmonary vascular disease
- Meticulous line care (also consider air filters for intravenous lines) to reduce risk of paradoxic embolus in patients who are cyanotic because of right-to-left shunts
- Adjustment of anticoagulant volume in tubes for some blood work in cyanotic patients
- Prevention of venous thrombosis
- Monitoring of renal and liver function
- Periprocedure anticoagulation
- Possible need for nonconventional drug dosing
- Increased prevalence of hepatitis C infection because of prior procedures and remote blood transfusions
- Developmental disability

Source: Stout et al. [87]. Reproduced with permission of Wolters Kluwer Health Inc.

ACHD indicates adult congenital heart disease; AP, anatomic and physiological; CHD, congenital heart disease; HF, heart failure.

KEY POINTS: HIGH-RISK PATIENT GROUPS

- Patients with pulmonary hypertension are at an increased risk of morbidity and mortality intraoperatively; it must be recognized that this risk extends into the postoperative period.
- Patients with Williams syndrome may have coronary artery abnormalities in the absence of significant supravalvular aortic stenosis that put them at increased risk for myocardial ischemia.
- The ECG should be monitored closely for signs of ischemia in high-risk patients; ST changes should be promptly addressed.

Intraoperative care

Monitoring

Standard American Society of Anesthesiologists (ASA) monitors provide adequate monitoring for the vast majority of children undergoing less invasive surgical or diagnostic procedures. When caring for healthy children who may be fearful of placing the ECG pads and NIBP cuff, it is common practice to apply these monitors after the initiation of an inhalation induction. Children with CHD should have baseline vital signs before induction, and increasing the frequency of NIBP determination from the default of once every 3 minutes should be considered. High-risk patients, such as those described in the previous section, or patients undergoing major orthopedic, intra-abdominal, or intrathoracic procedures are best managed with invasive arterial monitoring and/or central venous

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monitoring. Invasive arterial monitoring will assist in the early recognition of hypo- or hypertension, and arterial blood gas monitoring allows easy determination of acid–base status, electrolytes, and hemoglobin. There are many cardiac lesions that are sensitive to a reduction in preload, yet these same patients may manifest a reduction in pulmonary compliance with volume overload. In this situation, central venous monitoring is very useful and provides good vascular access for the delivery of vasoactive medications.

There are a number of newer monitors designed to measure cardiac output noninvasively. Some of these monitors have been validated against thermodilution or echocardiographic measurements of cardiac output. However, none of these new monitors have been shown to provide an early warning of a low cardiac output state that improves recognition and outcome. Near-infrared spectroscopy (NIRS) has been most widely studied. This monitor measures oxygen saturation of tissue approximately 2–4 cm beneath the probe. It was originally designed to determine cerebral oxygen saturation in the frontal cortex when the probe is applied to the forehead. It provides a noninvasive assessment of the regional oxygen supply–demand balance to the tissues over which the probe is applied (brain, kidney, gut). It is affected by tissue blood flow, arterial oxygen saturation, hemoglobin saturation, and the ratio of arterial to venous blood flow. These factors should be considered when interpreting changes in tissue oxygen saturation. As a continuous monitor, it has been shown to identify global hypoperfusion produced by a reduction in cardiac output due to a reduction in mixed venous oxygen saturation [89]. The monitor has been used to detect splanchnic ischemia in premature infants [90]. NIRS monitoring has also been shown to provide an early indication of reduced cardiac output after cardiac surgery [91]. It may therefore be a useful addition to routine noninvasive monitors for the child with CHD who has a greater risk of hemodynamic compromise, by providing an early warning and enabling a rapid response. However, no studies have determined the monitor's utility and ability to improve outcomes in the setting of noncardiac surgery. See Chapter 13 for a further discussion of monitoring techniques.

Anesthetic technique

The choice of anesthetic technique depends on the anticipated duration and the hemodynamic consequences of the planned surgery, the hemodynamic consequences of the patient's cardiac anatomy, and the patient's cardiac reserve. In general, patients with CHD are not tolerant of the myocardial depressant effects of higher concentrations of inhalational agents. Opioids are used to reduce the requirement of inhalational agent. See Chapter 6 for a discussion of the hemodynamic effects of anesthetic agents, and Chapter 21 for a discussion of hemodynamic management.

Regional anesthesia is not contraindicated unless the patient is taking anticoagulant medication, and regional anesthesia will allow a reduction in volatile agent requirement without the side-effects of opioid medications. Most patients have improved cardiac output from the sympathectomy that develops from central neuraxial blocks; the exceptions are the patient with aortic or mitral stenosis and those with obstructive cardiomyopathy.

Surgery

Many less invasive surgical procedures can be performed on an outpatient basis, even for ASA 3 and 4 patients. However, all high-risk patients should undergo surgery in a location where appropriate rescue can be performed. Even though complications are rare, the incidence of cardiac arrest or death is significantly greater among patients with CHD, and most surgical centers do not have appropriate rescue capability for these patients. Special consideration should be made for the high-risk population outlined earlier, and they should undergo noncardiac surgery in a location where rhythm disturbances are rapidly recognized and treated, resuscitative medications are present, and rescue with ECMO is available. When dealing with patients with systemic or supra-systemic pulmonary hypertension, inhaled nitric oxide should be immediately available to treat acute increases in pulmonary pressure.

Complex surgical situations

Laparoscopic surgery

Laparoscopic surgery has many benefits, including smaller incision, faster return of bowel function, decreased postoperative pain, and shorter hospital stays. This technique requires insufflation of carbon dioxide into the peritoneum. There has been concern that patients with CHD might not tolerate the hemodynamic effects of abdominal insufflation. For example, the pulmonary blood flow of shunted single-ventricle patients is dependent on PVR. The pneumoperitoneum can result in decreased ventilation due to increased intra-abdominal pressure with an associated increase in $PaCO_2$, absorption of carbon dioxide with an associated increase in $PaCO_2$, a decrease in preload and an increase in SVR. It should be noted that end-tidal CO_2 has been shown to be an inaccurate measure of $PaCO_2$ in patients with cyanotic CHD [92]. However, with close monitoring of blood gases and ventilator adjustments, low insufflation pressures of 8–12 mmHg, and blood pressure support, outcomes can be optimized [53, 93]. In must also be remembered that many patients with CHD have right-to-left intracardiac shunts from septal defects or complete intracardiac mixing; a large CO_2 embolus into the systemic arterial circulation (coronary and cerebral) can rapidly cause cardiovascular collapse or neurological injury in these patients.

The patient with a Fontan circulation requires adequate preload and normal PVR to maintain passive pulmonary blood flow. Concerns regarding a decrease in pulmonary blood flow due to the combination of positive pressure ventilation and abdominal insufflation, as well as an increase in PVR due to carbon dioxide absorption, make laparoscopic surgery appear higher risk in these patients. However, there have been several case reports and small case series noting stable hemodynamics with laparoscopic surgery in Fontan patients with good ventricular function, without the need to augment preload or administer vasoactive medication [94, 95]. For short procedures such as laparoscopic appendectomy or cholecystectomy, arterial and CVP monitoring has not been needed. We recommend discussing the potential need to convert to an open procedure with the surgeon, patient, and/or family prior to surgery. In addition,

insufflation should be gradual and the minimum intra-abdominal pressure utilized.

Hemodynamic changes with the release of pneumoperitoneum should also be anticipated. Studies in healthy children have shown that the release of pneumoperitoneum results in a decrease in SVR and blood pressure, and a decrease in preload due to redistribution of blood into the splanchnic bed and liver [96–98]. Groenewald and Latham report a cardiac arrest in a patient with supravalvular aortic stenosis immediately following release of pneumoperitoneum. It is suggested that patients, especially those at risk for myocardial ischemia, be monitored closely during this period, and that the release of intra-abdominal pressure be gradual [99].

Recent larger studies have examined the safety and outcomes of patients with CHD undergoing laparoscopic procedures with varying results. In a single-institution, retrospective review of 121 laparoscopic procedures and 45 open procedures in patients younger than 5 years with CHD, no significant differences were noted in complications or 30-day mortality between laparoscopic and open procedures. Eighty-seven percent of the patients in the laparoscopic group were infants, and single ventricle diagnosis did not affect outcome [100]. A 2016 study by Kim et al. utilized the American College of Surgeons National Surgical Quality Improvement Project Pediatric (ACS NSQIP-P) Database to compare complications, postoperative length of stay, and 30-day mortality in 3,684 patients less than 1 year of age with CHD undergoing either laparoscopic or open abdominal surgery. The laparoscopic group had a lower overall complication rate and a shorter length of stay with similar 30-day mortality [101]. Also using data from the ACS NSQIP-P Database, Chu et al. looked prospectively at 34,543 children aged 0–17 years with no, minor, major, or severe CHD undergoing laparoscopic surgery. They found that patients with minor CHD had similar mortality but increased 30-day morbidity compared to children with no CHD. In addition, patients with major or severe CHD had higher overall mortality and 30-day morbidity compared to children with no CHD. In fact, children with severe CHD were 12 times more likely to die compared with a matched patient without CHD when undergoing a laparoscopic procedure. The majority of deaths were in patients who were less than 12 months of age at the time of operation. A stepwise increase in postoperative reintubation rate was also observed as severity of CHD increased, possibly indicating limited physiologic reserve [102]. In a retrospective cohort study using the same database, matching patients less than 18 years old undergoing laparoscopic or open procedures, the authors found that in patients with minor CHD, laparoscopic surgery was associated with a lower 30-day mortality, in hospital mortality, and 30-day morbidity. The benefits were not as great or nonexistent for patients with major or severe CHD. However, length of stay and odds of transfusion were decreased for those undergoing laparoscopic procedures compared with open [103]. Herrick et al. looked retrospectively 5,527 patients older than 5 years with CHD undergoing laparoscopic or open procedures. The found that all-cause mortality and length of stay was lower for those undergoing laparoscopic procedures. By studying those >5 years old, the higher risk interstage and infant groups did not affect the data. Patients with Fontan physiology, who one might consider vulnerable to the effects of abdominal insufflation, were not found to be at increased risk of mortality when undergoing laparoscopic surgery compared with an open approach [104].

Otolaryngologic procedures

As reported by Sulkowski and Nasr, otolaryngologic procedures (along with general surgery procedures) are the most common noncardiac surgeries performed in pediatric patients with CHD [2, 3]. This may be expected as the incidence of congenital and acquired airway abnormalities in the CHD population is 8.5 and 9.7%, respectively. Risk factors for airway abnormalities include weight <10 kg, prematurity, the presence of a genetic syndrome, and certain CHD diagnoses (interrupted aortic arch, double aortic arch, arch anomaly, pulmonary artery abnormality, tetralogy of Fallot) [105]. The incidence of respiratory events such as bronchospasm, laryngospasm, difficult intubation, failed extubation and reintubation, and arterial desaturation in patients with CHD undergoing noncardiac procedures is 4.7%, and the odds ratio of having a respiratory event during an otolaryngological procedure is 2.65 [106]. Billings et al. reviewed neonatal microdirect laryngoscopies and bronchoscopies (MLB) over the 10-year period from 2002 to 2012. Of the 162 neonates undergoing MLB, 30.2% had a diagnosis of CHD. In this series, 84.3% of procedures were diagnostic and 15.7% were therapeutic. Patients with CHD had an increased incidence of complete rings, tracheal stenosis, bronchomalacia, abnormal bronchial anatomy, and vascular rings. The patients with CHD were also less likely to have tracheostomy and supraglottoplasty procedures and were more likely to require long-term intubation [107].

Anesthesia for microlaryngoscopy and bronchoscopy can be quite challenging in patients with CHD. The procedure is very stimulating itself, requiring significant depth of anesthesia, and the surgeon often prefers that the patient is breathing spontaneously to assess vocal cord mobility and dynamic airway changes and to delay desaturation. A period of hyperoxygenation and hyperventilation before turning the airway over to the otolaryngologist is helpful for delaying hypercarbia and desaturation during the procedure. Positive pressure ventilation can be supported via a jet port incorporated into the surgeon's laryngoscope and then via the bronchoscope. However, intermittent breaks for mask ventilation or ventilation via endotracheal tube may be necessary to improve oxygen saturations and decrease $PaCO_2$. Anesthetic depth can be achieved with various anesthetic agents including volatile anesthetic, propofol, ketamine, and dexmedetomidine. Whatever anesthetic technique is chosen, the anesthesiologist must maintain close communication with the otolaryngologist, and primary and secondary plans for managing the airway should be discussed before the procedure. Even though most otolaryngologists prefer spontaneous ventilation during rigid bronchoscopy, it is typically only required to assess vocal cord mobility. Once that portion of the examination is complete, the patient can potentially receive muscle relaxant and positive pressure ventilation, and the depth of anesthesia can be reduced.

Patients that are challenging to anesthetize for this procedure include shunt dependent patients, patients with cyanotic lesions and/or pulmonary hypertension, and those

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with poor myocardial reserve. These patients may not tolerate wide swings in PVR or the deep levels of anesthesia required for the procedure.

Spinal instrumentation

Children with CHD have a higher incidence of scoliosis than the general population due to congenital vertebral abnormalities, thoracotomies and sternotomies, neuromuscular issues related to a hypoxic event, or a syndrome associated with neuromuscular scoliosis [108]. As survival of patients with CHD, especially those with single ventricle lesions, has improved, it has become increasingly common to attend to noncardiac issues, such as scoliosis, which affect quality of life. In addition, correction of scoliosis and related improvement of cardiorespiratory factors are important for optimizing Fontan physiology and survival [108, 109].

Multiple studies report on the perioperative outcomes of patients with CHD undergoing spinal instrumentation with low mortality [108–115]. Perioperative complications were increased in patients with pulmonary hypertension [113], single ventricle physiology [109], and a large Cobb angle [109]. In a retrospective study of patients with CHD undergoing scoliosis repair, patients with a biventricular circulation had a 16% incidence of a significant perioperative event and a 32.3% incidence of any adverse event, compared with those with a single ventricle circulation with a 25% incidence of a significant perioperative event and a 68.8% incidence of any adverse event [109].

The complications experienced by single ventricle patients are largely related to increased blood loss and fluid shifts. In a retrospective review of 23 patients with single ventricle CHD undergoing scoliosis repair, 52% of the cohort experienced complications, with pleural effusion being the most common (54%) [108]. Blood loss is higher in the single ventricle population due to Fontan physiology which often necessitates a higher baseline CVP to encourage pulmonary blood flow and maintain cardiac output. Other factors such as positive pressure ventilation, hypoxemia, hypercarbia, hypothermia, and acidosis can also necessitate a higher CVP perioperatively. A higher CVP can result in more intraoperative and postoperative bleeding, more volume administration, and complications due to fluid shifts [109].

In order to reduce blood loss, many centers use a combination of control of blood pressure (mean arterial pressure 50–60 mmHg) and normovolemic hemodilution in patients without CHD. In general, these strategies are not encouraged in patients with CHD. Preoperative blood donation for autologous transfusion in this population has also been described [116]. Arterial blood pressure monitoring is standard; however, the use of CVP monitoring and intraoperative transesophageal echocardiography varies. Cerebral and somatic NIRS monitoring may be useful, as well.

Some of the larger retrospective case reviews spanning up to 25 years note that the incidence of adverse perioperative events and the amount of blood loss have decreased in more recent years. Improvements in perioperative care and strategies for mitigating risk include enhanced multidisciplinary discussion and planning, the routine use of antifibrinolytic medications (tranexamic acid), and a better understanding of how to care for this complex and fragile patient population. Przybylski et al. report a change in goal intraoperative mean arterial pressure from 50–60 to 65–75 mmHg over the course of the study [109]. Cohen et al. report a 67% complication rate without the use of tranexamic acid, and a complication rate of 36% with the use of the drug. Estimated blood loss of 69.8 cc/kg without tranexamic acid usage was reported compared with 26.1 cc/kg with tranexamic acid usage. The reduction in blood loss due to tranexamic acid can result in the need for decreased volume expansion and fewer complications due to fluid shifts (e.g., pleural effusions) [108].

Changes in surgical planning and conduct can also reduce blood loss and mitigate risk. The use of preoperative halo traction to improve the Cobb angle can reduce the length of the scoliosis surgery and the associated blood loss. Other strategies include careful attention to intraoperative time management, using two operative surgeons to work faster, and meticulous attention to hemostasis during the exposure [117].

KEY POINTS: INTRAOPERATIVE CARE

- Monitoring, anesthetic technique, and operative venue are dependent on the patient's disease and the procedure performed; hemodynamic instability should be anticipated.
- The hemodynamic effects of the creation and release of pneumoperitoneum should be anticipated; gradual, low-pressure insufflation and gradual release produce the least disturbance.
- Laparoscopic procedures can be safely performed in patients with CHD, provided there is meticulous attention to hemodynamic and ventilatory management by experienced providers.

Radiologic procedures

Magnetic resonance imaging and computed tomography

Anesthetic care is often required for diagnostic imaging of the patient with CHD, as patient immobility is frequently required for an adequate study. Cardiac magnetic resonance (CMR) and CT imaging of patients with CHD can provide valuable information about anatomy and function. MRI studies of the brain are commonly used to evaluate preoperative or postoperative neurologic abnormality or injury. The approach to reducing mobility for these studies varies from no anesthetic or sucrose, to sedation, to general anesthesia with spontaneous ventilation, to a general anesthetic with breath-holding. It is important to discuss requirements of the study with the radiologist and choose an appropriate plan based on the requirements and patient factors. The choice of CMR or CT imaging depends on the information desired, the potential need for general anesthesia, and the patient's perceived anesthetic risk vs. risk of radiation exposure.

Cardiac MRI can provide information regarding extracardiac arteries and veins, assessment of vascular or valvular flow, quantification of shunts, and assessment of myocardial

function. It is the imaging modality of choice for the evaluation of corrected tetralogy of Fallot, aiding in the determination of timing for pulmonary valve replacement by the measurement of right ventricular volumes. It can also be used for pre-Glenn or pre-Fontan evaluation of single-ventricle patients in lieu of cardiac catheterization [118, 119]]. Risks associated with catheterization, including vascular injury and cardiac tamponade, are removed, and patients are not exposed to ionizing radiation. Compared with diagnostic cardiac catheterization, imaging with CMR is associated with a decreased length of hospital stay [120]. CMR is also the imaging modality of choice for complex aortic coarctations that require further arch delineation [118] and for postsurgical evaluation after coarctation repair [121]. However, for coarctations that have been stented, there is often compete loss of signal, and evaluation for stent restenosis is not possible (Figure 35.5) [122]. CMR can also be performed to gather information regarding myocardial perfusion at rest and with stress using adenosine or dobutamine. CMR also has a role in diagnosing cardiomyopathies, even in pre-clinical stages [123].

Although there is associated exposure to ionizing radiation, cardiovascular CT is especially useful in imaging for vascular rings, where it is important to visualize related airway anatomy, pulmonary venous anatomy, or major aortopulmonary collateral arteries (MAPCAS), and in patients with metallic implants or CIEDs [123]. CT can also be used to evaluate coronary artery anomalies. Advances in CT technology and the introduction of second-generation, dual-source, high-pitch scanners have resulted in cardiovascular imaging that is associated with a significant decrease in exposure to ionizing radiation (equivalent to approximately five chest radiographs for most studies), faster scans, and an elimination of the need for breath-holding. For a significant number of patients, this obviates the need for a general anesthetic [124]. See Chapter 18 for a further discussion of the utility of CMR and CT imaging.



Figure 35.5 Magnetic resonance angiography in a patient who had stent placement for coarctation of the aorta. The stent generates a complete signal void (arrow) making it impossible to investigate for any restenosis within the stent. (Source: Sorensen et al. [122]. Reproduced with permission of Elsevier.)

Anesthetic techniques for these imaging studies vary in the depth and degree of airway manipulation. On the least invasive end of the spectrum, a feed and swaddle technique using a natural airway can be used for CT and shorter MR studies in neonates and young infants. Neonates have undergone cardiac CT angiography using a non-sedated, free-breathing, swaddling technique with excellent image quality [124]. Fogel et al. describe the successful CMR evaluation of aortic arch anomalies using this technique in infants less than 6 months of age. The CMR scanning time in this study was 6.2 ± 3.1 minutes [119]. The success of this strategy hinges on the presence of a cardiac imaging specialist in the control room to evaluate the images as each sequence is completed, and expeditious, efficient scanning that focuses on the diagnostic question.

Children are unlikely to stay still for a longer study without deep sedation or general anesthesia. Many centers employ deep sedation or general anesthesia via intravenous medications while maintaining a natural airway and spontaneous respiration. Medications used for this purpose include propofol infusion, dexmedetomidine infusion, and an infusion of a combination of propofol and ketamine. It is important to monitor the ECG, oxygen saturation, blood pressure, and end-tidal CO_2 during the sedation. End-tidal CO_2 can be monitored via a nasal cannula with a CO_2-monitoring port or through a port placed in a face mask.

Airway monitoring during the procedure is important, as airway obstruction can occur with general anesthesia or sedation. Airway compromise leading to increased $PaCO_2$ and/or decreased PaO_2 is poorly tolerated in some patients, especially those with pulmonary hypertension. These types of patients must be carefully monitored for developing hypercarbia and hypoxemia. A general endotracheal anesthetic is another option for longer procedures or when the airway control is crucial. In addition, it is possible to hold respiration for certain sequences. Another option includes a general anesthetic with a laryngeal mask airway.

The need for breath-holding when carrying out CMR varies according to the structures being imaged, the programmed sequences, and the experience and preference of the imaging team. The need for breath-holding increases as the size of the structures being imaged gets smaller. As many as eight breath-holds of 10–30 seconds are required for some diagnostic scans; the pathophysiological effects of this technique must be considered, i.e., the effect of preoxygenation and the lack of ventilation on shunted single-ventricle infants. Su et al. described an ECG and respiration-gated technique that obviates the need for breath-holding in the great majority of CMR studies. This technique allows selection of sedated, spontaneously breathing techniques for many patients [125].

It is critical to match the patient's cardiac lesion and cardiac function with an appropriate anesthetic. For example, a single ventricle with a modified Blalock–Taussig shunt is

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unlikely to tolerate a deep sedation with propofol. Propofol may lead to a decrease in mean arterial pressure, a decrease in driving pressure through the shunt, and an increase in PVR due to hypoxemia and hypercarbia from hypoventilation. This can result in a further decrease in shunt flow and dangerously low oxygenation saturations and can ultimately result in cardiac arrest (Figure 35.1).

Different institutions have published their experiences with anesthesia for CMR imaging and have found that the risk of adverse events is quite low [126, 127]. However, Stockton et al. reported a 28% incidence of adverse events, higher than that of the general pediatric population. It is important to recognize that practically all risks associated with MRI are related to the anesthetic. Single-ventricle patients are known to have increased risk of morbidity and mortality associated with anesthesia, and this includes anesthesia for CMR [5]. Particular attention should be paid to fasting times and inadequate preoperative hydration. Both Stockton et al. and Brown et al. report major adverse events including death prior to the anesthetic (thought to be dehydration-related), intraoperative cardiac arrest, and shunt thrombosis in this population. These adverse events led to a modification to the CMR protocol to include a preadmission for intravenous fluids and possible heparin administration prior to the study [12, 13]. At our institutions, we have a low threshold to admit these patients to the hospital after the scan for continuation of intravenous hydration as needed and for observation. Inadequate post-anesthetic oral intake and anesthesia-related physiologic alterations, including possible hypotension and reduced shunt flow, can result in significant consequences. Proper multidisciplinary planning, an experienced anesthesiologist, and vigilant perianesthetic care can help to minimize this risk.

Because of the high-risk nature of some CMR studies, appropriate planning for resuscitation and rescue should be in place. Any question about the stability of the patient during the MRI should necessitate stopping the scan and an evaluation of the patient, with a low threshold to remove the patient from the scanner room into an adjacent resuscitation area where ferromagnetic equipment does not pose a safety risk. Many congenital cardiac centers now have MRI incorporated into their catheterization laboratory suites, where rapid imaging after catheter interventions is possible. These scanners double as the CMR diagnostic scanners and have the added advantage of closer proximity to help and expertise to rescue the patient from a critical event.

Until recent years, the presence of a cardiac pacemaker was essentially an absolute contraindication to MRI scanning. However, there are now a number of MRI-compatible pacemaker systems that have been tested in adult patients and which are generally deemed to be safe. It is likely that these systems will be implanted in pediatric patients in the future. The risk benefit of MRI in this situation must be completely evaluated, and alternative means to obtain the imaging data should be sought. A protocol for the device, and the presence of experts in managing the devices during the MRI scan are essential if an MRI-compatible pacemaker procedure is planned [128]. Patients with non-MRI compatible systems may also be able to undergo MRI studies without patient or device complications. However, artifact related to the pacemaker or implantable cardiac defibrillator may render the study useless. This is particularly true for cardiac MRI. It is recommended that patients with non-MRI compatible systems be responsive and communicative during the procedure to monitor for complications [129].

Myocardial stress perfusion MRI is increasingly utilized in the pediatric population to evaluate ischemia due to coronary artery anomalies, both before and after surgical, catheter, or medical intervention. Indications include anomalous origin of the coronary artery from the aorta, myocardial bridge, Kawasaki disease, and postoperative evaluation of coronary re-implantation surgery such as arterial switch operation, anomalous origin of the left coronary artery from the pulmonary artery, and the Ross procedure [130, 131]. Myocardial perfusion is imaged before and after a pharmacological stressor, and assessed for reversible or permanent perfusion defects, to guide future therapy or assess results of past procedures. Several methods have been utilized to produce myocardial stress, including dobutamine infusion starting at 10 mcg/kg/min, and increasing to as high as 40 mcg/kg/min, with atropine added if heart rate increase (>150 bpm in teenaged patients) is not sufficient [130]. Another approach is to add a coronary artery vasodilator such as adenosine, or regadenoson, a selective alpha-2A receptor agonist [131]. Adverse hemodynamic events are a significant risk for these techniques, including ventricular arrhythmias, AV block, hypertension, and hypotension. Dyspnea, chest pain, flushing, headache, and nausea are frequent side effects in conscious patients. Defibrillation capability and resuscitation drugs must be in close proximity during these procedures, in addition to a plan to remove the patient from Zone IV of the MRI scanner for resuscitation. Many patients undergoing myocardial stress perfusion MRI are older and can tolerate an unsedated scan and comply with instructions to breath-hold. Younger patients requiring sedation can potentially receive propofol with a natural airway, but because most of these procedures will require breath-holding, general anesthesia with a laryngeal mask airway or endotracheal tube is often required. In a series of 224 pediatric dobutamine stress cardiac MRI, median patient age was 14 years and weight 58 kg [130]. Sedation was required in 17% of patients; and there were no major adverse events (cardiac arrest, myocardial infarction, ventricular arrhythmia), and 14% of patients had minor adverse events. In a pediatric series of 46 patients undergoing regadenoson stress cardiac MRI, median age was 9 years (range 2 months to 14 years), and 67% required sedation [131]. No patient experienced a major adverse event but there was a 20% incidence of minor events, including 9 with hypotension of which 8 required pharmacologic intervention with phenylephrine.

Lymphatic mapping and intervention

Lymphatic disorders in CHD include a number of conditions that are common sources of morbidity and mortality in patients with single ventricle physiology including pleural effusions, chylothorax, plastic bronchitis, ascites and protein losing enteropathy. Dynamic Contrast-enhanced Magnetic Resonance Lymphangiography (DCMRL) has emerged as a technique for the identification of lymphatic abnormalities,

and percutaneous (transabdominal or transhepatic) access of lymphatic vessels allows for the treatment of these lymphatic disorders by coiling or embolization (see Chapter 30).

The patients undergoing these procedures are largely single ventricle patients who are compromised from a respiratory standpoint, and they may be significantly debilitated. They require immobility for the duration of the procedure, and thus general endotracheal anesthesia is required. These patients may be on chronic diuretic therapy and may be hypovolemic and/or prone to electrolyte derangements. In addition to judicious volume administration, inotropic and/or vasopressor support may be indicated. Invasive arterial blood pressure monitoring may be helpful, and recovery in the ICU should be strongly considered due to complications or escalation of care in 25% of patients having a lymphatic intervention. Other procedures may be performed during the same anesthetic such as direct laryngoscopy and bronchoscopy in patients with plastic bronchitis or esophagogastroduodenoscopy in patients with protein losing enteropathy. Preoperative multidisciplinary planning is essential for the optimized outcome of these fragile patients [132].

KEY POINTS: MRI, CT, AND LYMPHATIC MAPPING AND INTERVENTION

- Risk associated with imaging is almost entirely anesthesia-related.
- Airway monitoring is critical; hypercarbia and hypoxemia can lead to cardiac arrest in high-risk patients, especially those with pulmonary hypertension.
- High-risk patients may require preoperative admission and hydration and/or postoperative admission and monitoring for imaging procedures requiring anesthesia.

Postoperative considerations

Intensive care unit vs. general inpatient unit

Inpatient postoperative recovery may take place in an intensive care setting or on a general inpatient unit. The decision about the postoperative setting should take a number of factors into consideration, including the cardiac diagnosis, the complexity of surgery, and potential postoperative difficulties. The decision to leave the trachea intubated at the end of the case necessitates an ICU admission.

The shunted single-ventricle circulation is fragile, and the risks and benefits of extubation must be weighed carefully. An extubated patient may develop apnea, hypoventilation, hypoxemia, hypercarbia, acidosis, and/or poor pain control; this may be catastrophic in a shunted single ventricle. In a series of five patients with HLHS after stage I palliation undergoing laparoscopic Nissen fundoplication, four were left intubated at the end of the operation. All were transferred to the ICU for recovery, and the remaining four patients were extubated on postoperative day 1. All had good outcomes [93].

Watkins et al. studied perioperative outcomes of 36 patients with HLHS after stage I palliation undergoing fundoplication and gastrostomy. Most patients were extubated in the OR and recovered on an in-patient unit. A substantial number of these patients developed cardiorespiratory instability postoperatively, and an escalation in care was required. During the study period, due to unplanned ICU admissions in this population, a policy was made that all patients with HLHS after stage I palliation should recover in an ICU after a general anesthetic [133].

In most other patients with CHD, recovery on a general inpatient unit is appropriate. However, patients should be monitored closely for respiratory difficulties, hemodynamic instability, desaturation, or arrhythmia, all of which can be poorly tolerated in the patient with CHD.

Home discharge criteria

It is possible to perform outpatient procedures on patients with CHD, but considerations should include the cardiac disease and stability of physiology, the type of procedure, and potential perioperative complications. Christensen et al. reported data on the anesthetic management and outcome in patients with surgically corrected dextro-transposition of the great arteries undergoing noncardiac surgery [134]. In this series of 50 procedures, 71% of patients who had undergone arterial switch operation (corrective repair) and 60% of patients who had undergone atrial switch operation (physiologic repair), were discharged home on the day of the procedure.

It must be recognized, however, that mild complications of anesthesia or surgery, including dehydration due to nausea and vomiting, poor intake of fluids by mouth, or bleeding, can result in serious morbidity for intravascular volume-sensitive patients with CHD [17]. In addition, as stated earlier, the perioperative risk of patients with pulmonary hypertension extends into the post-anesthesia period [55, 57]. These patients should not be discharged home on the day of surgery.

KEY POINTS: POSTOPERATIVE CONSIDERATIONS

- High-risk patients, such as patients with HLHS after the Norwood procedure, are commonly cared for in the ICU after a procedure due to their fragile circulation.
- Well-compensated patients with CHD can be discharged home on the day of surgery.
- Patients with pulmonary hypertension should be observed carefully after anesthesia and surgery.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

2 Nasr VG, Staffa SJ, Faraoni D, DiNardo JA. Trends in mortality rate in patients with congenital heart disease undergoing noncardiac surgical procedures at children's hospitals. Sci Rep 2021;11:1543. Nasr et al

describe the decline in mortality associated with patients with congenital heart disease undergoing noncardiac procedures over recent years and the potential factors leading to this favorable trend.

3 Sulkowski JP, Cooper JN, McConnell, et al. Variability in noncardiac surgical procedures in children with congenital heart disease. J Pediatr Surg 2014;49:1564–9. The authors report on the volume and type of noncardiac surgery performed in children who underwent cardiac surgery in the first year of life, helping to define the scope and need for specialized anesthetic care.

4 Maxwell BG, Wong JK, Kin C, Lobato RL. Perioperative outcomes of major noncardiac surgery in adults with congenital heart disease. Anesthesiology 2013;119:762–9. Using the National Inpatient Sample database, the authors report on the perioperative risk associated with adult congenital heart disease patients undergoing noncardiac surgery.

39 Forshaw N, James I. Anaesthesia for children with left ventricular assist devices indergoing noncardiac surgery. Br J Anaesth Educ 2018;18:371–6. The unique perioperative considerations of the pediatric patient with left ventricular assist device undergoing noncardiac surgery are reviewed in this educational piece.

40 Navartnam M, Maeda K, Hollander SA. Pediatric ventricular assist devices: Bridge to a new era of perioperative care. Pediatr Anesth 2019;29:506–18. This review is especially useful for those seeking to be more comfortable with monitoring and managing pediatric VAD patients undergoing cardiac or noncardiac surgery.

55 Latham GJ, Yung D. Current understanding and perioperative management of pediatric pulmonary hypertension. Pediatr Anesth 2019;29:441–56. This is a great review of the pathophysiology and treatment of a high risk disease, as well as really useful advice for perioperative management.

59 Twite MD, Stenquist S, Ing RJ. Williams syndrome. Pediatric Anesthesia 2019;29:483–90. This paper reviews the recent Williams syndrome literature and provides useful information for planning the perioperative care of this high risk population.

82 Lei Lei E, Heggie J. Adult congenital heart disease and anesthesia: an educational review. Pediatr Anesth 2021;31:123–31. A thourough understanding of the challenges associated with caring for the adult patient with congenital heart disease undergoing cardiac and noncardiac surgeries is critical for optimizing outcome.

108 Cohen LL, Przybylski R, Marshall AC, et al. Surgical correction of scoliosis in children with severe congenital heart disease and palliated single ventricle physiology. Spine 2021;46:E791–6. This review of 23 patients with single ventricle physiology who underwent spine surgery at a single institution focuses on the improved complication rates and decrease in blood loss over the study period.

132 Jobes DR, Brown LA, Dori Y, et al. Lymphatic imaging and intervention in a pediatric population: anesthetic considerations. Pediatr Anesth 2018;28:507–12. This article provides a thorough discussion of the anesthetic implications of this increasingly common and complex procedure in a fragile patient population.

CHAPTER 36

Cardiac Intensive Care

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Introduction

The pediatric cardiac intensive care unit (CICU) serves as the primary destination for critically ill children with congenital and acquired heart disease. It provides an expert model of care by bringing the broad range of specific expertise to the bedside of every CICU patient. Ideally, this allows the cardiac intensivist to engage in collaborative and dynamic decision-making that involves anesthesiologists, cardiac surgeons, interventionalists, imaging specialists, electrophysiologists, and heart failure/advanced cardiac therapies specialists, thus serving to provide highly effective and efficient care delivery to patients.

In contrast to general pediatric intensive care, the majority of CICU admissions are planned. With preoperative and precatheterization review and fetal echocardiography, it is possible and necessary to plan most admissions and their potential need for CICU resources. It is important to recognize that as survival outcomes have improved in children with congenital or acquired heart disease as a result of the current paradigms in management, the proportion of medical cardiac (MC) and unplanned CICU admissions will be expected to increase over time [1, 2].

Collaboration among CICUs and increased emphasis on quality improvement have significantly improved the outcomes of children with critical heart disease in the CICU setting. Efforts from multi-institutional collaborations (e.g., the Pediatric Cardiac Critical Care Consortium [PC[4]], which currently has over 65 CICUs submitting data to its registry) has provided a better understanding of case-mix and outcome variability among CICUs. Figure 36.1 shows multi-institutional data from PC[4] summarizing CICU admissions by age group, illness category (MC, surgical cardiac [SC]), and admission indication from 2018 to 2020.

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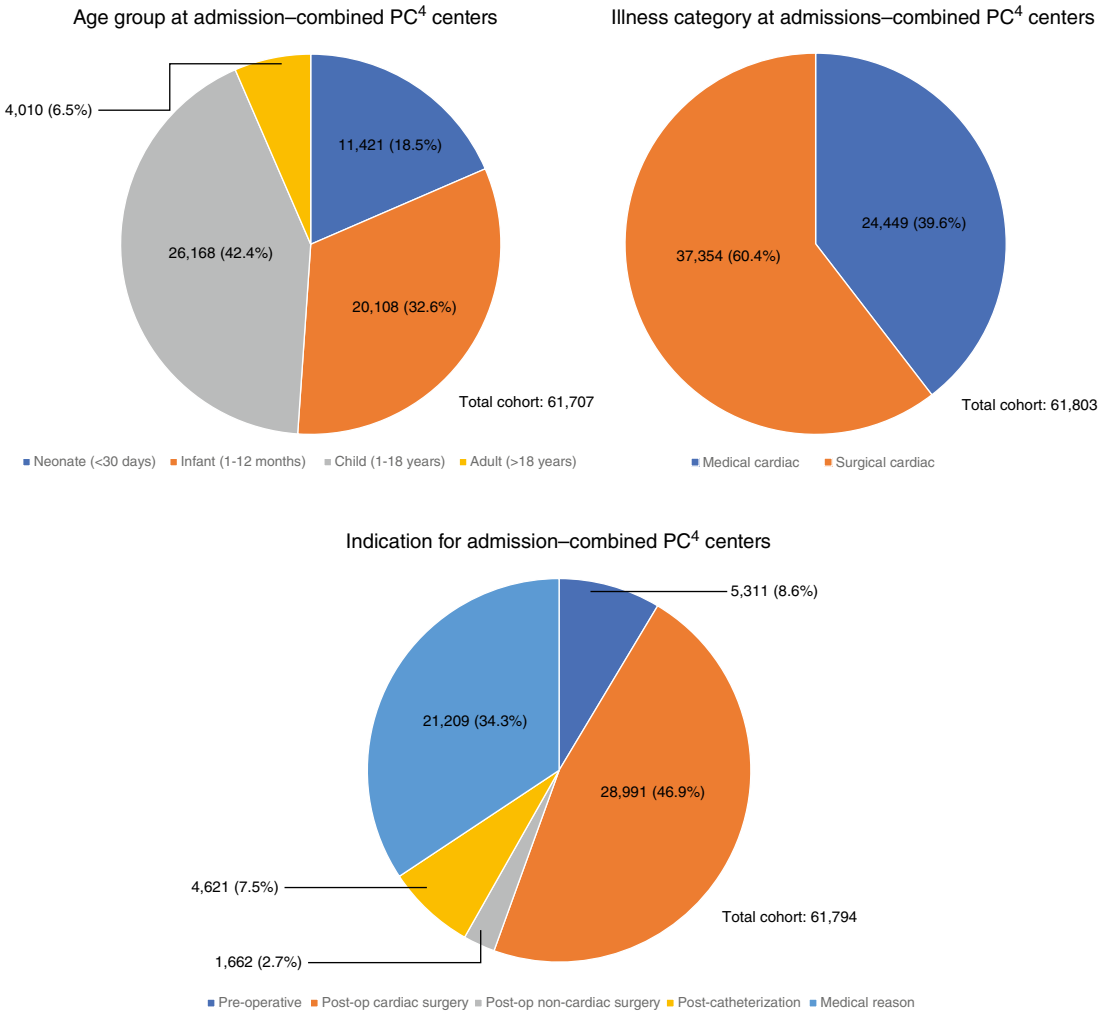


Figure 36.1 Pediatric intensive care unit admission categories from all centers that contribute data to the Pediatric Cardiac Critical care Consortium (PC[4]), including 66 centers at time of data collection. Categories evaluated: age group, illness category, indication for admission. Timeframe: January 1, 2018 to December 31, 2020. PC4, Pediatric Cardiac Critical care Consortium. (Source: Data obtained from the Pediatric Cardiac Critical care Consortium (PC[4]).)

Pathophysiology of specific congenital cardiac defects and implications

A thorough understanding of the pathophysiology of congenital cardiac defects is essential when managing these patients in the CICU. This will influence not only the preoperative management strategy for stabilization and/or resuscitation prior to surgery, but also preparations for the impact of preexisting physiologies such as cyanosis, pressure overload, and volume overload on myocardial performance and recovery after surgery. Understanding the changes in physiology achieved intraoperatively in SC patients is equally important for identifying expectations and the anticipated course in the CICU. In the presence of hemodynamically-significant residual intracardiac lesions after surgery, the accompanying alterations in pulmonary blood flow, systemic perfusion, and ventricular compliance may significantly affect recovery and length of stay (LOS) in the CICU.

Intercirculatory mixing, complete mixing, and streaming

Confusing terminologies are often used interchangeably to describe common preoperative and postoperative physiologies. It is important for the care provider to understand the essential elements of the circulation in order to react appropriately to perturbations.

Intercirculatory mixing lesions

Patients with D-transposition of the great arteries (D-TGA) have parallel circulations: the deoxygenated systemic venous blood returns to the right ventricle (RV) and is ejected through the aorta while oxygenated pulmonary venous blood is returned to the left ventricle (LV) and is ejected into the pulmonary artery (PA) (Figure 36.2). Although the figure depicts simple transposition anatomy, transposition *physiology* can occur with other anatomic defects such as "Taussig-Bing" type double-outlet right ventricle, where a subpulmonary

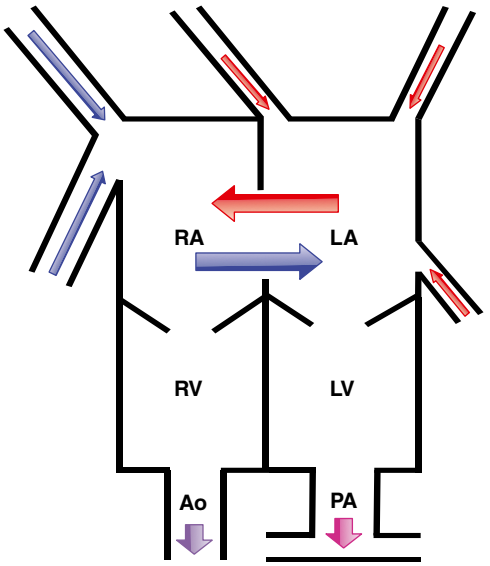


Figure 36.2 The anatomy and physiology of D-TGA. The diagram shows the typical stable circulation in unoperated D-TGA. The desaturated systemic venous (SV) blood (blue arrows) and fully saturated pulmonary venous (PV) blood (red arrows) require free mixing at the atrial level (often after a BAS) resulting in anatomically equivalent, left-to-right and right-to-left shunting. As a result, the saturations show the pattern where $SV_{sat} < Ao_{sat} < PA_{sat} < PV_{sat}$. Ao, aorta; BAS, balloon atrial septostomy; D-TGA, D-transposition of the great arteries; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; sat, O_2 saturation.

position of the ventricular septal defect (VSD) and malposition of the great arteries create an unfavorable streaming pattern resulting in parallel intracardiac circulation similar to D-TGA. Transposition *physiology* is the term used for this parallel circulatory pattern where PA oxygen saturation is greater than the aortic oxygen saturation. Such a circulation is not compatible with survival over time unless there is adequate intercirculatory mixing allowing for the deoxygenated systemic venous blood into the pulmonary circulation (PA), as well as the oxygenated pulmonary venous blood into the systemic circulation (aorta) [3]. Although 25–50% of patients with D-TGA have a VSD, the presence of a VSD does not guarantee adequate intercirculatory mixing, as mixing occurs most effectively at the atrial level. Newborns with D-TGA, irrespective of whether they are diagnosed antenatally or postnatally, can present with profound cyanosis in the absence of respiratory distress due to inadequate mixing. Such patients should be transported to the CICU after commencing intravenous (IV) prostaglandin E_1 (PGE_1) to maintain a patent ductus arteriosus (PDA) as an additional location for mixing. After confirmation of the diagnosis of D-TGA with a restrictive or intact atrial septum, a balloon atrial septostomy (BAS) can be performed at the bedside or in the cardiac catheterization laboratory to improve intercirculatory mixing and systemic oxygen delivery. If the atrial communication is restrictive, administration of usual therapies to improve pulmonary blood flow (e.g., supplemental oxygen, inhaled nitric oxide) are often detrimental if used as ongoing preoperative management strategies. These therapies can generate left atrial hypertension, leading to increasing pulmonary congestion and worsening pulmonary compliance with further impairment of atrial-level mixing. Once an adequate atrial septal defect (ASD) is created, systemic oxygen delivery improves as mixing increases from left to right (saturated pulmonary to desaturated systemic) across the ASD. Subsequently, patients can have the PGE_1 infusion discontinued and wean and extubate to await an elective repair with the arterial switch operation within the first week of life [4]. Some patients with D-TGA may remain hypoxemic despite creation of an unrestrictive atrial communication; such patients are often dependent on PGE_1 infusion in the preoperative period to maintain systemic saturations >65% [5]. The failure of adequate mixing at the atrial level may reflect not only differences in ventricular function, ventricular filling, and/or ventricular end-diastolic pressures (ventricular compliance), but may also be secondary to unfavorable streaming effects. There may also be an element of rebound pulmonary hypertension from PGE_1 discontinuation that reduces the volume of pulmonary blood flow without affecting the amount of intercirculatory mixing. Some investigators have suggested a protracted weaning protocol for PGE_1 to mitigate this effect [6]. See Chapter 29 for further discussion of D-TGA.

Complete mixing lesions

Complete mixing lesions represent a variety of anatomic entities that have a common chamber where pulmonary and systemic venous return completely mix before exiting. The conventional terminology for this is *single ventricle physiology* because it refers to a physiology in which the PA saturation and aortic saturation are equal. These lesions can have either ductal-dependent pulmonary blood flow (e.g., tricuspid atresia, pulmonary atresia with intact ventricular septum, or pulmonary atresia with VSD) or ductal-dependent systemic blood flow (e.g., hypoplastic left heart syndrome [HLHS], double-inlet left ventricle [DILV]). Although the majority of these lesions will require a palliative single ventricle surgical strategy, some patients with single ventricle physiology have two anatomically-adequate ventricles, allowing for an initial septation procedure (e.g., truncus arteriosus, tetralogy of Fallot [TOF] with pulmonary atresia). This is important when considering the systemic oxygen saturation (SaO_2) targets in managing these patients. The traditional targets of SaO_2 of 75–85%, partial pressure of O_2 (PaO_2) of 35–45 mmHg, mixed venous O_2 (MvO_2) saturation, and/or near-infrared spectroscopy (NIRS) of 50–60%, along with oxygen extraction fraction of ~25% together with appropriate blood pressure for age, systemic vascular resistance (SVR) state, and adequate markers of end-organ function (e.g., lactate level, urine output, clinical examination), are important when trying to balance pulmonary blood flow (Q_p) and systemic blood flow (Q_s) in a preoperative or postoperative patient with limited combined ventricular output. When combined ventricular output is not a limiting factor (e.g., preoperative patients with tricuspid atresia, those with truncus arteriosus), it is important to recognize that strict management of Q_p/Q_s balance is unnecessary in the absence of respiratory embarrassment or signs of inadequate systemic oxygen delivery (DO_2). See Chapter 30 for further discussion of single ventricle lesions.

Streaming

Streaming is the phenomenon where systemic venous blood (or pulmonary venous blood) can pass through to the

systemic circulation (or pulmonary venous blood to the pulmonary circulation) due to specific anatomic abnormalities that result in an anatomic chamber that is common to both circulatory systems (e.g., a common atrium, the absence of common arterial septum, truncus arteriosus, double-outlet right ventricle). This streamed blood may or may not be completely mixed before it reaches the arterial outlet. If it is incompletely mixed, the physiology is likely to be that of *transposition physiology* ($PA_{sat} > Ao_{sat}$), whereas streaming that is completely mixed will be *single ventricle physiology* ($PA_{sat} = Ao_{sat}$) [3].

Shunts

Shunting between the pulmonary and systemic circulations can be intracardiac (across an ASD or a VSD) or extracardiac (across a PDA, aortopulmonary window, decompressing venovenous collaterals, aortopulmonary collateral, or arteriovenous malformation). Depending on the size of the communication and the differential pressures and resistances between the pulmonary and systemic circulations, patients may have decreased or increased pulmonary blood flow and may be either cyanotic or acyanotic, respectively.

Increased pulmonary blood flow

Shunts that increase pulmonary blood flow may occur either between the atria, ventricles, or the great arteries, and they can be simple or complex. The degree of restriction across these shunts also affects their potential clinical significance. The most common clinical signs seen with increased pulmonary blood flow are tachypnea, respiratory distress, tachycardia, difficulty feeding in neonates/infants, failure to thrive, and diaphoresis.

Simple shunt

The amount of flow across a "simple" left-to-right shunt depends on the size of the defect and the balance between pulmonary vascular resistance (PVR) and SVR. It is important to understand that this is a physiologic term and has no direct relationship to specific diagnoses (Table 36.1). Therefore, patients who have a simple shunt may have:

1. A normal SaO_2 with two ventricles, such as a large VSD, complete atrioventricular canal (CAVC), and large PDA
2. A normal SaO_2 with a single ventricular outflow trunk and two ventricles (truncus arteriosus)
3. A "low" SaO_2 (80–95%) and two ventricles (D-TGA with large VSD)
4. A "low" SaO_2 (75–85%) and single ventricle (tricuspid atresia or following a Blalock–Taussig (BT) shunt such as in a modified Norwood procedure).

If the simple shunt is "unrestrictive," the physiologic consequence for all the above mentioned diagnoses will be the same, i.e. excessive pulmonary flow and volume overload to the ventricle receiving the increased pulmonary venous blood flow plus secondary respiratory embarrassment. The degree of shunt will be determined not by the size of the defect, but rather by the relationship between SVR and PVR [7, 8]. The clinical manifestation will also be the same, namely congestive heart failure (CHF) and pulmonary hypertension, although some patients will be cyanotic and others acyanotic, depending on the degree of intracardiac mixing and streaming.

On the other hand, for a simple "restrictive" shunt, when the orifice or size of the shunt is small, the size of the communication is the limiting factor determining the increase in pulmonary blow flow; relative SVR and PVR may have little or no impact in this situation. In this circumstance, there is minimal overload to the ventricle receiving pulmonary venous flow, and the pulmonary circulation is protected from excess pressure and flow; as a result, patients may be relatively asymptomatic and present at an older age with nonspecific symptoms such as recurrent respiratory infections or failure to thrive.

Table 36.1 Simple shunts: defects or surgical procedures contributing to an increased pulmonary blood flow/systemic blood flow (Q_p/Q_s)

	Acyanotic	Cyanotic
Two ventricles	ASD VSD CAVC DORV	D-TGA/VSD PA/VSD
Single ventricle		TA ± TGA HLHS DORV/MA Norwood procedure BT shunt
AP connection	PDA Truncus arteriosus AP window	PA/MAPCA

AP, aortopulmonary; ASD, atrial septal defect; BT, Blalock–Taussig; CAVC, complete atrioventricular canal; D-TGA, dextro-transposition of the great arteries; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; MA, mitral atresia; MAPCA, major aortopulmonary collateral artery; PA, pulmonary atresia; PDA, patent ductus arteriosus; TA, tricuspid atresia; VSD, ventricular septal defect.

Complex shunt

In the presence of additional pulmonary or systemic outflow obstruction, the ratio of pulmonary-to-systemic blood flow (Q_p/Q_s) is determined by the size of the orifice and the outflow gradient as well as SVR and PVR. The obstruction may be fixed (valvular aortic or pulmonary stenosis) or dynamic (some forms of TOF, tricuspid atresia with normally related great arteries and a dynamically restrictive muscular VSD).

Clinical consequences of increased pulmonary-to-systemic blood flow ratio

If the increase in pulmonary blood flow and pressure persist over months to years, structural changes occur within the pulmonary vasculature until eventually PVR becomes irreversibly elevated [7–9]. The time course for developing this pathology, termed pulmonary vascular obstructive disease (PVOD), depends in part on the degree of volume overload to the pulmonary circulation, degree of pressure overload to the pulmonary circulation, exposure of the pulmonary vascular bed to cyanosis, and duration of exposure to these factors in the setting of a shunt [10]. Changes may be evident by 4–6 months of age in some lesions (e.g., large VSD or CAVC). The progression can be more rapid when the volume and pressure overload to the pulmonary circulation are increased, such as with truncus arteriosus. When pulmonary blood flow is increased in the absence of pressure overload,

such as in simple secundum ASD, PVOD typically develops much more slowly, if at all during childhood.

As PVR decreases in the first days to weeks after birth, and the hematocrit falls to its lowest physiologic value, the increased left-to-right shunt and anemia-related high-output state result in volume loading on the systemic ventricle along with CHF. A typical pressure–volume loop for a volume-loaded ventricle is shown in Figure 36.3. The end-diastolic volume is increased and the end-diastolic pressure–volume line displaced to the right indicating reduced contractility. The time course over which irreversible ventricular dysfunction develops is variable, but if surgical/catheter intervention to correct the volume overload is undertaken within the first 2 years of life, residual dysfunction is uncommon [11]. The volume load on the systemic ventricle and increased end-diastolic pressure contribute to increased pulmonary edema by increasing pulmonary venous and lymphatic pressures. Decreased lung compliance and increased airway resistance occur secondary to small airways compression by distended vessels [12, 13]. This manifests clinically in infants with both tachypnea and increased work of breathing. If tracheally intubated for mechanical ventilation, the lungs may feel stiff on hand ventilation, deflate slowly, and exhibit an obstructive pattern; poor compliance may be apparent during mechanical breaths.

Besides cardiomegaly on chest radiograph, the lung fields are usually congested and hyperinflated. Ventilation/perfusion mismatch contributes to an increased alveolar-to-systemic arterial ($A\text{-}aO_2$) gradient and dead space ventilation [14]. Minute ventilation is, therefore, increased, primarily by an increase in respiratory rate. PA and left atrial enlargement may compress mainstem bronchi causing lobar collapse. PA and left atrial dilation may be seen on chest radiograph in the form of widening at the hilum from PA contour enlargement and upward splaying of the left mainstem bronchus from distortion due to left atrial dilation. Furthermore, tachycardia, increased fussiness/agitation, and poor weight gain may be seen secondary to increased myocardial oxygen demand in response to pulmonary overcirculation and ventricular volume loading.

It is important to appreciate that such clinical scenarios can be present even after surgery in patients who have significant residual intracardiac shunts that cause an increase in Q_p/Q_s. This may manifest during the early postoperative course as low cardiac output syndrome (LCOS) (see the "Myocardial Dysfunction and Hemodynamic Monitoring" section) or become apparent some days after surgery with an inability to wean from mechanical ventilation or a persistent requirement for vasoactive support.

Decreased pulmonary blood flow

Reductions to pulmonary blood flow from structural heart disease are ultimately related to intracardiac right-to-left shunting. The basis for this may be pulmonary outflow obstruction (supravalvar, valvar, subvalvar, or a combination of these), subpulmonary ventricle inflow obstruction (tricuspid stenosis or atresia), or the inability to generate adequate antegrade pulmonary blood flow (Ebstein anomaly, tricuspid valve dysplasia). In patients with noncardiac diseases, such as persistent pulmonary hypertension of the newborn (PPHN), sustained elevations in PVR result in intracardiac (or ductal) right-to-left shunting.

Pulmonary mechanics and lung volumes are generally normal in patients with reduced pulmonary blood flow. Dead space ventilation is increased, although minute

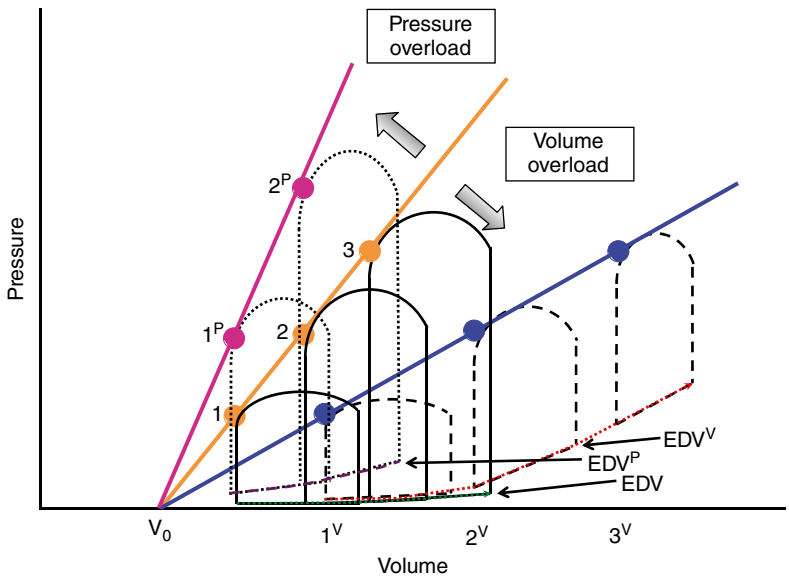


Figure 36.3 Pressure–volume relationships. In a gradual afterload increase on a ventricle that can compensate (orange line moving from 1 to 3), the stroke volume is maintained at the cost of higher intracavitary pressure (wall stress) and lower ejection fraction. Generally, this does not require a higher EDP (dotted green line). In the failing myocardium (blue line), stroke volume can only be maintained (initially) at a higher EDP (dotted red line); ultimately stroke volume will be compromised (moving from 1^v to 3^v). An acute afterload increase on a ventricle (pink line) results in a lower stroke volume (moving from 1 to 1^p to 2^p), despite compensatory mechanisms to augment stroke volume with a higher EDP (dotted purple line). EDP, end-diastolic pressure; EDV, end-diastolic volume.

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ventilation is only slightly increased to maintain normocapnia, and the A-aO_2 gradient may be increased as well. The lung fields appear oligemic on chest radiograph. Some patients may have impairments in pulmonary mechanics due to anatomic interactions between cardiovascular structures and the tracheobronchial tree. One such group are patients with TOF and absent pulmonary valve (APV) syndrome who can have massively dilated branch PAs; in the setting of a freely regurgitant pulmonary valve orifice, the RV and branch PAs become volume loaded and dilate, leading to compression of the large and small airways. These patients have significant gas-trapping and expiratory flow limitations, which is a frequent cause of their respiratory failure. Surgical repair during the newborn period is often required to treat respiratory failure in this scenario. Often in neonates with TOF with APV, early prone positioning with positive pressure ventilation (PPV) is required to alleviate bronchial compression and achieve adequate gas exchange; however, emergent sternotomy in unrepaired patients may still be required in some cases to alleviate airway compression despite mechanical ventilation and proning [15, 16].

Target systemic oxygen saturation level

The postoperative target SaO_2 level is important to establish, as it will guide assessment and therapeutic intervention (Table 36.2). Potential causes of abnormally low SaO_2 include:

1. Pulmonary venous desaturation (normal is 95–99% in ambient air) indicating an intrapulmonary shunt secondary to primary pulmonary pathology (e.g., alveolar edema/consolidation or pleural effusion)
2. A reduction in effective pulmonary blood flow, such as from pulmonary outflow obstruction, reduced aortopulmonary shunt flow from mechanical obstruction, increased PVR, intracardiac right-to-left shunt, or decompressing venovenous collaterals (e.g., from a high-pressure superior vena cava to the inferior vena cava in a Glenn circulation)
3. A reduction in arterial oxygen content (CaO_2), principally in patients who have mixing of systemic and pulmonary venous blood at the atrial-level or single ventricle physiology. The reduction in CaO_2 may be due to low MvO_2 level (such as reduced oxygen delivery due to impaired cardiac output or increased oxygen extraction) or a low oxygen carrying capacity (reduced hematocrit).

Table 36.2 Factors to consider in a postoperative cardiac surgery patient with an arterial oxygen saturation lower than the anticipated range

Etiology	Considerations
Low FiO_2	Inappropriately low-set oxygen concentration for delivery
	Failure of oxygen delivery device
Pulmonary vein desaturation	Impaired diffusion
	Alveolar process: edema, infection
	Restrictive process: effusion, atelectasis, pneumothorax
	Intrapulmonary shunt
	RDS
	Pulmonary AVM
	PA-to-PV collateral vessel(s)
Reduced pulmonary blood flow	Anatomic RV outflow obstruction
	Anatomic pulmonary artery stenosis
	Increased PVR
	Atrial-level right-to-left shunt
	RV hypertension
	Restrictive RV physiology (low compliance)
	Severe tricuspid regurgitation
	Large fenestration (modified Fontan operation)
	Intra-atrial baffle leak
	Reduced aorta pulmonary shunt flow
	Ventricular-level right-to-left shunt
	RV hypertension and residual VSD
Low dissolved O_2 content (SV and TGA physiology)	Low mixed venous oxygen level
	Increased O_2 extraction: hypermetabolic state
	Decreased O_2 delivery: low cardiac output state
	Anemia

AVM, arteriovenous malformation; FiO_2, fractional inspired concentration of oxygen; O_2, oxygen; PA, pulmonary artery; PV, pulmonary vein; PVR, pulmonary vascular resistance; RDS, respiratory distress syndrome; RV, right ventricle; SV, single ventricle; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Outflow obstruction

Severe LV or RV outflow obstruction in the newborn may be associated with ventricular hypertrophy and vessel hypoplasia distal to the level of obstruction. If there is complete or near-complete outflow obstruction, mixing or shunting at the ASD and/or VSD level is required to maintain systemic cardiac output (CO) with adequate arterial oxygen content.

A typical pressure–volume loop from a chronic pressure load on the ventricle is shown in Figure 36.3. The end-diastolic pressure is elevated and the end-systolic pressure volume line is shifted to the left, reflecting increased contractility in the compensated state (purple line), with an upwards shift along the new slope reflecting a higher afterload state (from 1^P to 2^P). Maintenance of preload, stability in afterload, adequate contractility, and normal sinus rhythm are important to prevent a fall in CO or coronary hypoperfusion in states of increased ventricular afterload. Since the time course to develop significant ventricular dysfunction is longer in patients with chronic pressure overload compared to chronic volume overload, symptoms of CHF are uncommon, unless obstruction is severe or prolonged.

In the immediate postoperative period, it is important to evaluate both systolic and diastolic ventricular function in a previously obstructed but still hypertrophied ventricle.

1. A hyperdynamic state may be present following LV outflow reconstruction. This will be manifest by systemic hypertension and should be treated promptly to reduce myocardial work and protect surgical suture lines, especially those in the aorta.
2. Systolic dysfunction of a hypertrophied ventricle may be apparent early after cardiac surgery secondary to myocardial ischemia and ventricular dysrhythmias. Ischemia

may occur particularly if there has been a long aortic cross-clamp time, inadequate myocardial protection with cardioplegia solution, or hypothermia. In the case of the RV, dysfunction may be related to a right ventriculotomy, direct injury to a coronary artery (e.g., a conal branch running across the RV outflow tract), air embolism, or due to inadequate myocardial protection with cardioplegia, hypothermia, or local cooling strategies. This should be evaluated and treated in the postoperative period with inotropic and/or inodilator support (i.e., dopamine or epinephrine, milrinone, and nitric oxide in the case of the RV). The evaluation of ventricular function includes echocardiography and potentially cardiac catheterization to assess hemodynamics and investigate potential coronary complications that may require reintervention.

3. Diastolic dysfunction is usually manifest as a poorly compliant or stiff ventricle that is hypertrophied. It may contract well, but it is unable to relax and fill effectively during diastole. On the left side of the heart, this is usually manifest as left atrial hypertension with either pulmonary edema, atrial dysrhythmias, or pulmonary hypertension. On the right side of the heart, an increase in RV end-diastolic pressure is demonstrated by right atrial hypertension and elevated central venous pressures along with clinical signs such as atrial arrhythmias, lower SaO_2 from a right-to-left shunt (e.g., across a patent foramen ovale [PFO] or ASD), hepatomegaly, diffuse edema (especially in neonates), pleural effusions, and ascites. In the postoperative period, patients with diastolic dysfunction may benefit from lusitropic agents (e.g., milrinone) to improve myocardial relaxation, are typically dependent on adequate preload to maintain sufficient CO, do not tolerate aggressive diuresis because of preload dependency, and may not tolerate rapid volume resuscitation due to the inability of the noncompliant ventricle to accept a large increase in intravascular volume. Patients with RV diastolic dysfunction (e.g., TOF) may benefit from early tracheal extubation, as PPV can increase RV afterload and hinder RV preload. Significant and untreated postoperative tachycardia in this population can also lead to a limitation in CO and increase in myocardial oxygen consumption.

KEY POINTS: PATHOPHYSIOLOGY

- Newborns with CHD may present with cyanosis or shock. This may result from transposition physiology ($PA_{sat} > Ao_{sat}$) or single ventricle physiology ($PA_{sat} = Ao_{sat}$) depending on the balance of mixing, streaming, and shunting.
- As PVR drops in the first few days and weeks of life, CHF may develop in children with large left-to-right shunts.
- Hypoxemia in single ventricle patients may develop from pulmonary venous desaturation, systemic venous desaturation, inadequate pulmonary blood flow, or suboptimal oxygen carrying capacity.

Airway and ventilation management

In all of the examples of mixing, shunting, and outflow obstruction described earlier, the mode and method of mechanical ventilation may have a substantial impact on hemodynamics and systemic perfusion. Particularly for neonates and infants, cardiorespiratory interactions are essential to recognize during postoperative management. While changes in the PaO_2, partial pressure of carbon dioxide ($PaCO_2$), and pH are well recognized to affect PVR, the mean airway pressure and changes in lung volume during PPV will also affect PVR, preload, and ventricular afterload. In addition to evaluating the adequacy of mechanical ventilation settings by arterial blood gas and chest radiography, it is important that ventilator settings be continually evaluated and adjusted according to hemodynamic response.

Airway management

Intubation of the trachea in a neonate or young infant with CHD may elicit undesirable hemodynamic and metabolic responses. Appropriate anesthetic techniques are thus desirable to secure the airway.

Traditionally, uncuffed endotracheal tubes (ETTs) were recommended for children younger than 8 years given the narrowest part of the airway is at the level of the cricoid cartilage. However, more recent studies suggest there is no difference between airway complications with cuffed and uncuffed tubes, particularly in the era of microcuff tubes (high-volume, low-pressure cuff) [17, 18]. If a significant air leak exists around the ETT, lung volume, and in particular functional residual capacity (FRC), will not be maintained and fluctuations in gas exchange can occur. During the ventilator weaning process, a significant leak will also increase the work of breathing for some neonates and infants. In these situations, it is, therefore, preferable to exchange the ETT for a larger-sized tube or to change to a cuffed tube. In contrast, an ETT that is smaller than usual may be necessary in certain situations. This is particularly the case in patients with other congenital defects such as Down syndrome (trisomy 21). Tracheal stenosis may also occur in association with some congenital cardiac defects such as a PA sling. Extrinsic compression of the bronchi may occur by the PA or a dilated left atrium. This may be suspected by persistent hyperinflation or lobar atelectasis on a chest radiograph.

Mechanical ventilation

Altered lung mechanics and ventilation/perfusion abnormalities are common problems in the immediate postoperative period [14]. Patients who have $Q_p/Q_s > 2:1$ may have cardiomegaly and congested lung fields on chest radiograph. Patients who have an elevated left atrial pressure may demonstrate signs of pulmonary venous hypertension and pulmonary edema. Additional considerations include the surgical incision and lung retraction, increased lung water following cardiopulmonary bypass (CPB), possible pulmonary reperfusion injury, CPB-induced surfactant depletion in neonates, and restrictive defects from atelectasis and pleural effusions.

In general, patients with limited physiologic reserve should not be weaned from mechanical ventilation until hemodynamically stable and any problems contributing to an increase in intrapulmonary shunt and altered respiratory mechanics have improved.

Cardiorespiratory interactions

Cardiorespiratory interactions vary significantly between patients and throughout the postoperative course. Consequently, the mode of ventilation must be matched to the hemodynamic status of each patient to achieve an adequate CO and gas exchange. The influence of PPV on preload and afterload is shown in Table 36.3. Frequent modifications to the mode and pattern of ventilation may be necessary during recovery after surgery, with attention to changes in lung volume, compliance, and airway pressure.

Influence of lung volume

Changes in lung volume have a major effect on PVR, which is lowest at FRC. Both atelectasis and hyperinflation may result in a significant increase in PVR, as shown in Figure 36.4 [19–21]. At low-tidal volumes, alveolar collapse occurs because of reduced interstitial traction on alveolar septae. In addition, radial traction on extra-alveolar vessels such as the branch PAs is reduced, therefore reducing the cross-sectional diameter. Conversely, hyperinflation of the lung may cause stretching of the alveolar septae and compression of alveolar vessels.

An increase in PVR increases the afterload or wall stress on the RV, compromising RV function and contributing to decreased LV compliance secondary to interventricular septal shift (from right to left). In addition to low CO, signs of RV dysfunction, including tachycardia, tricuspid regurgitation, hepatomegaly, ascites, and pleural effusions, may be observed.

Table 36.3 Effect of a positive pressure mechanical breath on afterload and preload to the pulmonary and systemic ventricles

	Afterload	Preload
Pulmonary ventricle	Elevated Effect: ↑ RVEDp ↑RVp ↓Antegrade PBF ↑ PR and/or TR	Reduced Effect: ↓ RVEDV ↑ RAp
Systemic ventricle	Reduced Effect: ↓ LVEDp ↓ LAp ↓ Pulmonary edema	Reduced Effect: ↓ LVEDV ↓ LAp Hypotension

LAp, left atrial pressure; LVEDp, left ventricle end-diastolic pressure; LVEDV, left ventricle end-diastolic volume; PBF, pulmonary blood flow; PR, pulmonary regurgitation; RAp, right atrial pressure; RVEDp, right ventricle end-diastolic pressure; RVEDV, right ventricle end-diastolic volume; RVp, right ventricle pressure; TR, tricuspid regurgitation.

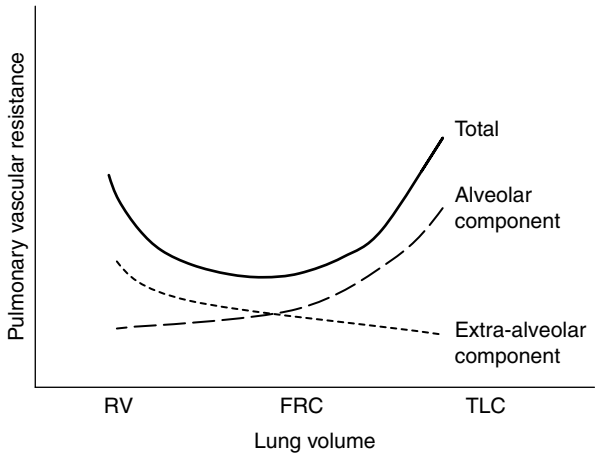


Figure 36.4 Lung volume impacts pulmonary vascular resistance. In the diagram above, there is a marked decrease in pulmonary vascular resistance when lung volume increases from RV (residual volume) to FRC (functional residual capacity). This is primarily a function of alveoli strutting open extra-alveolar vessels as they are expanded (drop in extra-alveolar resistance; dotted line). Further increases in lung volume from FRC to TLC (total lung capacity) cause increases in pulmonary vascular resistance. This is mainly due to compression of intra-alveolar vessels by air-trapping (alveolar component; dashed line). Total pulmonary vascular resistance is minimized at FRC (solid line).

Influence of intrathoracic pressure

An increase in mean intrathoracic pressure during PPV decreases preload to both pulmonary and systemic ventricles, but has opposite effects on afterload of each ventricle [22–24].

Right ventricle

The increase in pressure in the right atrium and reduction in RV preload that occurs with PPV may reduce CO. Normally, RV diastolic compliance is high and the pulmonary circulation is able to accommodate changes in flow without a large change in pressure. An increase in mean intrathoracic pressure increases the afterload on the RV from direct compression of extra-alveolar and alveolar pulmonary vessels. This has a number of clinical consequences (Table 36.3). An increase in afterload causes an increase in RV end-diastolic pressure and myocardial work, which may lead to myocardial ischemia in a patient with limited coronary perfusion. An example of the increase in RV pressure during a positive pressure breath is demonstrated in Figure 36.5.

Patients with normal RV compliance and no residual volume or pressure load on the ventricle following surgery usually show little change in RV function from the alteration in preload and afterload that occurs with PPV. However, these effects can be magnified in patients with RV hypertrophy and those with restrictive RV physiology. At particular risk are neonates requiring a right ventriculotomy for repair of TOF with pulmonary atresia or truncus arteriosus; concentric RV hypertrophy poses additional risk. While systolic RV function may be preserved in these situations, the ventricle often demonstrates diastolic dysfunction with increased RV end-diastolic pressure and impaired RV filling.

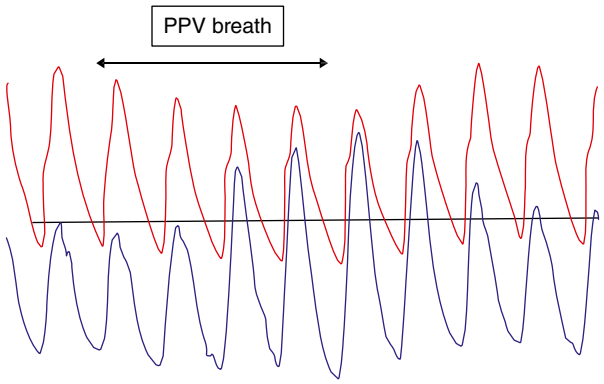


Figure 36.5 Positive pressure ventilation effects on the right ventricle. Simultaneous tracings of aortic (red) and right ventricle (blue) pressure waveforms during positive pressure ventilation (PPV) in a child with pulmonary artery stenosis. Note the increase in right ventricular pressure to approximately systemic (aortic) level during mechanical inspiration when the afterload on the right ventricle is increased.

It is important to emphasize the potentially deleterious effects of mechanical ventilation on RV function. The aims should be to ventilate with a mode that enables the lowest possible mean airway pressure while maintaining adequate lung volume and limiting potential secondary injury to the lung. In patients with lung disease, such as pneumonia, adult respiratory distress syndrome, or lung disease of prematurity, a low tidal volume strategy (4–6 mL/kg) using a low peak inspiratory pressure, short inspiratory time, increased intermittent mandatory ventilation (IMV) rate, and higher levels of positive end-expiratory pressure (PEEP) is recommended. However, this strategy is also associated with a higher mean intrathoracic pressure and afterload on the RV, which reduces antegrade pulmonary blood flow. In contrast, a strategy utilizing larger tidal volumes (10–12 mL/kg), lower IMV rates (15–20 breaths/min), and larger peak inspiratory pressure–PEEP difference with a shorter inspiratory time (0.4–0.5 seconds) may be preferential in patients with restrictive RV.

Left ventricle

LV preload is also affected by lung volume. Pulmonary blood flow and, therefore, preload to the systemic ventricle may be reduced by an increase or decrease in lung volume secondary to alteration in radial traction on alveolar and extra-alveolar vessels.

The systemic arteries are under higher pressure and not exposed to radial traction effects during inflation or deflation of the lungs. Therefore, changes in lung volume will affect LV preload, but the effect on afterload is dependent on changes in intrathoracic pressure alone.

In contrast to the RV, a major effect of PPV on the LV is a reduction in afterload. Using the law of Laplace, wall stress is directly proportional to the transmural LV pressure and the radius of curvature of the LV and inversely proportional to the thickness of the ventricle. The transmural pressure across the LV is the difference between the intracavity LV pressure and the surrounding intrathoracic pressure. Assuming a constant arterial pressure and ventricular dimension, an increase in intrathoracic pressure, as occurs during PPV, will reduce the transmural gradient and, therefore, wall stress on the LV (Figure 36.6). Therefore, PPV and PEEP can have significant beneficial effects in patients with LV systolic dysfunction or failure (Table 36.3).

Patients with LV dysfunction with an increased end-diastolic volume and pressure can have impaired pulmonary mechanics secondary to increased lung water, decreased lung compliance, and increased airway resistance. The work of breathing is increased, and neonates can fatigue early because of their limited respiratory reserve. A significant proportion of total body oxygen consumption is directed at the increased work of breathing (especially the diaphragm) in neonates and infants with LV dysfunction, contributing to poor feeding and failure to thrive. Therefore, PPV has an additional benefit in patients with significant volume overload and systemic ventricular dysfunction by reducing the work of breathing and oxygen demand.

Positive end-expiratory pressure

The use of PEEP in patients with CHD has two important effects: recruiting FRC and O_2 reserve capacity and redistributing lung water from alveolar septal regions to the more compliant perihilar regions. Gas exchange is improved, and the work of breathing reduced. This is particularly important in patients with a volume load, ventricular dysfunction, and elevated end-diastolic volume. PEEP should, therefore, be used in all mechanically ventilated patients following congenital heart surgery. However, excessive levels of PEEP can be detrimental by increasing afterload on the RV. Usually 3–5 cmH_2O of PEEP will help maintain FRC and redistribute lung water without causing hemodynamic compromise.

The use of PPV and PEEP in patients who have undergone either a Glenn or Fontan procedure (cavopulmonary anastomosis) has also been debated. In this group of patients, pulmonary blood flow is nonpulsatile and depends on the pressure gradient between the superior vena cava and the pulmonary venous atrium. During PPV, pulmonary blood flow can be diminished, and during a Valsalva maneuver and at high levels of PEEP, retrograde pulmonary blood flow may be demonstrated by Doppler echocardiography. Nevertheless, the beneficial effects of using low-pressure PPV and PEEP to achieve desired lung volume, minute ventilation and gas exchange following the Fontan procedure are apparent at the bedside. This strategy rarely contributes to a clinically significant decrease in effective pulmonary blood flow and, in fact, may be more than offset when compared to the elevations in PVR related to a strategy of low-volume spontaneous ventilation [25, 26].

Alternative modes of ventilation and respiratory support

The use of high-frequency oscillatory ventilation (HFOV) has been beneficial in the management of hypoxemic and hypercapneic respiratory failure where the goal is to optimize systemic oxygen delivery while minimizing lung injury. The mean airway pressure may be higher than when using conventional ventilation, but can be well tolerated hemodynamically, provided preload is maintained. There

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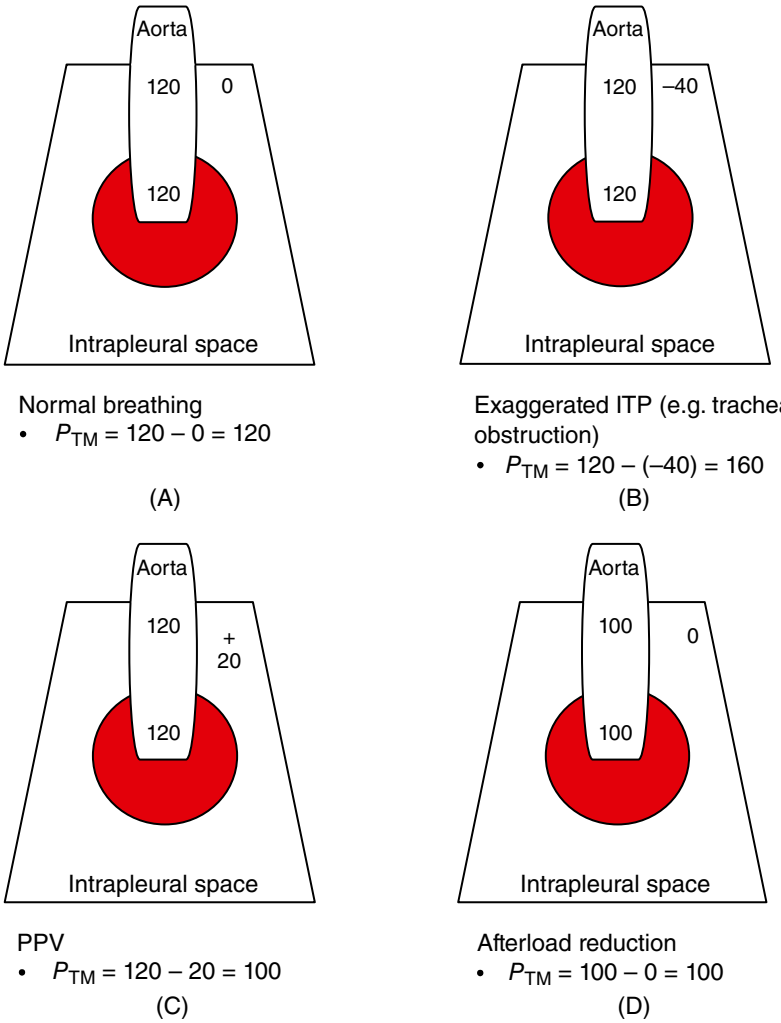


Figure 36.6 Transmural aortic pressure affects left ventricular afterload. By the law of Laplace, the transmural aortic pressure (P_{TM}) is affected by intrapleural pressure. During normal breathing (A), there is very little effect of the intrapleural pressure on P_{TM} and thus left ventricular afterload. Generation of pathologic degrees of negative intrapleural pressure (as with severe airway obstruction or decompensated heart failure) significantly increases left ventricular afterload (B). Provision of positive pressure ventilation (PPV) (C) or pharmacologic afterload reduction (D) can both independently reduce left ventricular afterload. ITP, intrathoracic pressure.

is no defined and agreed-upon indication for HFOV in the literature, but it should be considered in the setting of ventilatory failure with a rising $PaCO_2$ and mean airway pressures >14 cmH_2O in neonates and >16 cmH_2O in older children using conventional ventilator modes. Recent data using propensity matching suggest that HFOV might reduce the length of ventilation after CHD surgery in neonates and infants [27].

Noninvasive ventilation (NIV) using either mask CPAP, bilevel positive airway pressure (PAP), or high-flow nasal cannula (HFNC) can be a helpful adjunct in patients who are tachypneic with an increased work of breathing and those requiring improved oxygenation through maintenance of FRC. In addition, it can potentially improve CO and ventricular function by reducing wall stress and afterload. NIV also avoids the attendant risk of endotracheal intubation, including escalating sedation requirements and ventilator-associated pneumonia and tracheitis [28].

HFNC with humidified oxygen at flow rates of between 3 and 10 L/min can be used to help minimize work of breathing and caloric expenditure in patients recently weaned from mechanical ventilation and/or those awaiting surgery. Although the PEEP delivered through this mode is variable, this mode is a helpful adjunct, especially in small patients with resting lung volumes approaching closing capacity [29].

Early extubation

Early extubation, generally defined as extubation within 6 hours of surgery, has been described for various cardiac lesions. Possible advantages of this strategy include fewer pulmonary complications, reduced sedative and analgesic use, shorter ICU and hospital LOS, and reduced resource utilization. Early extubation can be especially beneficial in patients with restrictive RV physiology or absent subpulmonary ventricle (cavopulmonary connection with the Fontan procedure). Some centers have employed collaborative learning models to develop clinical guidelines for early extubation practices. Although this improved rates of early extubation, ICU LOS did not change [30]. One notable exception is in the Fontan

patient; not only will spontaneous ventilation improve pulmonary blood flow and CO, fast-track extubation in the operating room (OR) is an important predictor of postoperative LOS [31, 32]. Furthermore, rates of successful early extubation vary across institutions, but increased specialized nursing in the CICU may improve outcomes [33]. NIV, including HFNC or PAP, has also been utilized, particularly in high-risk, postcardiac surgical patients, to mitigate the risk of extubation failure. However, there is limited evidence regarding NIV utilization in pediatric CICUs to inform best practice [34].

Weaning from mechanical ventilation

Weaning from mechanical ventilation is a dynamic process that requires continued reevaluation. While most patients following uncomplicated congenital cardiac surgery will wean without difficulty, some patients with borderline cardiac function and/or residual defects may require prolonged mechanical ventilation and a slow weaning process. As spontaneous ventilation increases during the weaning process, swings in mean intrathoracic pressure may substantially alter afterload on the systemic ventricle. The transition to spontaneous ventilation may cause a sudden increase in wall stress, which then contributes to an increase in end-diastolic pressure and volume, leading to pulmonary edema and low CO. Inotropic agents, vasodilators, and diuretics should be continued throughout the ventilator weaning process and early after extubation to maintain stable ventricular function as mechanical respiratory support is reduced.

The method of weaning is variable. Most patients can be weaned using either a volume-limited or pressure-limited mode by simply decreasing the IMV rate. Guided by physical examination, hemodynamic criteria, respiratory pattern, and arterial blood gas measurements, the mechanical ventilator rate is gradually reduced. Patients with limited hemodynamic and respiratory reserve may demonstrate tachypnea, diaphoresis, and reduced tidal volumes as they struggle to breathe spontaneously against the resistance of the ETT. The addition of pressure- or flow-triggered pressure or volume support breaths above PEEP at a level related to the size of the ETT decreases this resistance and is often beneficial in reducing the work of breathing.

A flow-triggered mode of pressure or volume support, with a backup ventilator rate if the patient becomes apneic (assist-control mode), is particularly useful for neonates and infants who received prolonged ventilation following surgery or have a residual volume or pressure load compromising ventricular function. Patients are often more comfortable weaning in this mode and have reduced work of breathing; the level of pressure support is adjusted according to their gas exchange, respiratory rate, and tidal volume.

Numerous factors can contribute to the inability to wean from mechanical ventilation following congenital heart surgery (Table 36.4). As a general rule, however, suspected residual defects causing either a volume or pressure load must be excluded first by echocardiography or cardiac catheterization.

Table 36.4 Factors contributing to the inability to wean from mechanical ventilation after congenital heart surgery

Residual cardiac defects
• Volume and/or pressure overload
• Myocardial dysfunction
• Arrhythmias
Restrictive pulmonary defects
• Pulmonary edema
• Pleural effusion
• Atelectasis
• Pneumothorax
• Chest wall edema
• Phrenic nerve injury
• Ascites
• Hepatomegaly
Airway
• Subglottic edema and/or stenosis
• Retained secretions
• Vocal cord injury
• Extrinsic bronchial compression
• Tracheobronchomalacia
Metabolic
• Inadequate nutrition
• Diuretic therapy
• Sepsis
• Stress response

Restrictive defects

Pulmonary edema, pleural effusions, and persistent atelectasis may delay weaning from mechanical ventilation. Residual chest and abdominal wall edema, ascites, and hepatomegaly can each limit chest wall compliance and diaphragmatic excursion. Chest tubes and peritoneal catheters may be necessary to drain pleural effusions and ascites, respectively.

If atelectasis persists, bronchoscopy is often useful to remove obstructive secretions and to diagnose any extrinsic compression from enlarged PAs, a dilated left atrium, or conduits. Patients rarely fail from mild mechanical or dynamic airway compression alone and often have contributory residual lesions [35].

Phrenic nerve injury can occur during cardiac surgery secondary to traction, thymic resection, thermal injury from electrocautery, or direct transection as a complication of extensive aortic arch and pulmonary hilar dissection. Diaphragmatic paresis (no motion) or paralysis (paradoxical motion) should be investigated in any patient who fails to wean and extubate successfully [36]. Increased work of breathing, abnormal respiratory mechanics, increased $PaCO_2$, and/or an elevated hemidiaphragm on chest radiograph following extubation (i.e., off positive pressure support) are all consistent with diaphragmatic dysfunction. Ultrasonography or fluoroscopy is used to confirm abnormal diaphragmatic movement. For an accurate diagnosis, these imaging investigations must be performed off positive pressure support. Additional discussion of airway management, ventilation, and extubation strategies is presented in Chapters 23 and 24.

Fluids and nutrition

Fluid restriction and aggressive diuretic therapy are commonly used early after cardiac surgery with CPB and can result in metabolic disturbances and insufficient nutritional intake. A hypochloremic, hypokalemic metabolic alkalosis with

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secondary respiratory acidosis is a common complication from high-dose loop diuretic use and can delay the ventilator weaning process. The need for and dosing of diuretic agents should be continually reevaluated. Furthermore, many patients will have limited reserve secondary to preoperative failure to thrive; maintaining adequate nutrition/caloric intake is challenging, given the catabolic state of patients early after surgery with CPB.

Analgesia and sedation

Adequate analgesia and sedation are necessary to optimize synchronization with the ventilator and maintain hemodynamic stability as well as provide comfort. Depending on the age of the patient, the magnitude of the operation, any residual defects, and the preoperative condition, there is potential for both escalation and prolongation of these requirements.

Appropriate analgesia can often be provided with a low-dose opioid infusion. Although escalation may seem necessary based on clinical concerns, in particular hypertension or tachycardia, these are often secondary to inadequate sedation rather than from pain. A benzodiazepine or nonopioid drug such as dexmedetomidine is useful in these circumstances. The appropriate drug must take into account the anticipated duration of mechanical ventilation and the need to titrate rapidly to drug effect. When early extubation is planned, short-acting adjuncts such as dexmedetomidine, ketorolac, and acetaminophen are useful [37]. A propofol infusion can be a helpful strategy in selected patient groups for whom agitation during rapid weaning is a sign of intolerance to airway stimulation as opposed to failure to wean from other causes. However, a propofol infusion must be used with caution because of potential hemodynamic complications and the risk of propofol infusion syndrome [38]. Oversedation can impair the weaning process because of somnolence, leading to hypoventilation, failure to trigger the ventilator, and inability to protect the airway.

For patients who have required mechanical ventilation for several days to weeks, and, therefore, received higher cumulative doses and a range of analgesic and sedative medicines, rapid weans from analgesics and sedatives can result in withdrawal symptoms. These symptoms can often be confused with pulmonary or cardiac reasons for failure to wean, as respiratory and hemodynamic symptoms may predominate. It is important to have a systematic analgesia/sedation weaning protocol that incorporates the timing of weaning with objective withdrawal assessment and knowledge of pharmacokinetics [39].

Sepsis

Sepsis is a particular risk following cardiac surgery for a number of reasons, including the immunomodulating effects of CPB, risk factors such as an open sternum, the use of vascular catheters for invasive monitoring and IV medications, and liberal use of broad-spectrum antibiotics. Sepsis can be a cause of failure to wean from mechanical ventilation because of its systemic effects, the associated increased work of breathing, and the imbalance between oxygen demand and delivery.

Airway

Bronchospasm can complicate mechanical ventilation and the weaning process. While this may reflect intrinsic airway disease, bronchospasm can also result from increased airway secretions, airway infection, and extrinsic airway compression. Treatment with inhaled or systemic bronchodilators may be beneficial, although they should be used with caution because of their chronotropic and tachyarrhythmic potential.

The sudden onset of bronchospasm with increased peak inspiratory pressure and difficulty with hand ventilation should raise the immediate concern for acute ETT obstruction or tension pneumothorax. Bronchospasm in patients with labile PVR may reflect acute pulmonary hypertension, and treatment is directed at maneuvers to lower PVR and improve systemic CO.

Postextubation stridor may be due to mucosal swelling of the large airway, and treatment with dexamethasone before extubation can be beneficial to reduce edema in patients who have required prolonged use of an ETT. Stridor following extubation can initially be treated with nebulized epinephrine, which promotes vasoconstriction and decreases airway hyperemia and edema. If reintubation is necessary, a smaller ETT should be used.

Vocal cord paresis or paralysis can result from surgical trauma to the recurrent laryngeal nerve and can be a cause of upper airway obstruction. Surgery on or near the aortic arch (e.g., repair of coarctation or interrupted aortic arch, and Norwood stage I palliation) is a risk factor for this injury, with symptoms ranging from weak or hoarse cry to significant upper airway obstruction requiring tracheal intubation. Diagnosis is typically made with either awake flexible nasolaryngoscopy or laryngeal ultrasound of the neck; both imaging procedures can be performed at the bedside [40].

The ability to clear secretions and the potential for nosocomial infection are additional concerns in patients who have been ventilated for an extended period of time. Inability to clear secretions because of sedation, bulbar and vocal cord dysfunction, ineffective cough following prolonged intubation, and poor nutritional state with muscle fatigue will result in atelectasis and respiratory failure. Frequent chest physiotherapy and nasopharyngeal suction are beneficial, provided that patients are hemodynamically stable with adequate gas exchange. Furthermore, the use of nasopharyngeal CPAP and/or HFNC can be beneficial by reducing the work of breathing; however, these patients have limited reserve, and frequent reassessment is essential.

KEY POINTS: AIRWAY AND VENTILATION IN CHD

- The lowest PVR is achieved by ventilating around FRC.
- PPV will reduce RV output by reducing preload and increasing RV afterload. This may be clinically deleterious in patients without a subpulmonary pumping chamber or with a restrictive RV.
- PPV will reduce work of breathing, LV afterload, and myocardial work.
- Failure of ventilator weaning can be due to a residual cardiac lesion or can be noncardiac in origin.

Myocardial dysfunction and hemodynamic monitoring

Assessment of cardiac output

The accurate assessment of the postoperative patient's CO should be a focus of management in the CICU. Recognition and effective management of LCOS is critical, as this clinical entity is associated with increased morbidity, including longer duration of mechanical ventilatory support and CICU/hospital LOS, and mortality [41, 42]. Data from physical examination, routine laboratory testing, bedside hemodynamic and electrophysiologic monitoring, echocardiography, and occasionally bedside CO determination are typically sufficient to manage patients optimally. If patients are not progressing as expected and low CO persists, a systematic evaluation for residual lesions should occur. The imaging assessment for residual lesions typically occurs noninvasively first by echocardiography, with the addition of computed tomographic (CT) angiography, if needed. When a more complete assessment with direct hemodynamic measurements is required, then cardiac catheterization should be undertaken.

The systemic CO is defined as the product of ventricular stroke volume (in L/beat) multiplied by heart rate (in beats/min). The ventricular stroke volume is determined chiefly by three factors: afterload (the resistance to ventricular emptying), preload, and myocardial contractility. CO is usually indexed to body surface area (BSA, in m^2) because it is a function of body mass. Thus, CO/BSA is designated as cardiac index (CI, in $L/min/m^2$). The CI varies inversely with age: normal values in children at rest are 4.0–5.0 $L/min/m^2$, whereas the normal resting CI at age 70 years is 2.5 $L/min/m^2$ [43, 44].

Postoperative patients with low CO can present with a variety of abnormalities on physical examination, bedside monitoring, and laboratory assessment. These manifestations of low CO are listed in Table 36.5. Clinical signs on examination include cool extremities and diminished peripheral perfusion, tachycardia, hypotension, oliguria, and hepatomegaly. An increase in the arterial to mixed venous oxygen saturation (A-VO_2) difference of >30% and a lactic acidosis provide biochemical evidence for low CO. The atrial pressure is a useful measure to follow, and either an increase or decrease could be observed in LCOS. Factors that should be considered when evaluating the atrial pressure following surgery are shown in Table 36.6.

The mechanism(s) underlying low CO in a specific patient can be related to either one or a combination of factors following surgery. Strategies for treating the patient with a low CO should focus on optimizing the balance between oxygen consumption (VO_2) and delivery (DO_2). In LCOS, oxygen and metabolic demand should be minimized by maintaining an adequate depth of analgesia and sedation, including chemical paralysis, in order to avoid movement, reduce muscle tone, and limit oxygen consumption. Strict avoidance of hyperthermia from any cause is essential, and in some circumstances, mild hypothermia may be preferable, although the effect of peripheral vasoconstriction and increase in SVR from hypothermia could have an adverse impact on myocardial wall stress and oxygen requirements.

Table 36.5 Manifestations of low cardiac output

Physical examination
- Mental status: lethargy or irritability
- Vital signs:
  - Core hyperthermia (often associated with peripheral vasoconstriction)
  - Tachycardia or bradycardia
  - Tachypnea
  - Hypotension (for age and weight)
  - Narrow pulse pressure
- Peripheral perfusion:
  - Pale or mottled skin color and cool skin temperature
  - Prolonged (>3 seconds) distal extremity capillary refill time
  - Poorly palpable pulses
- Signs of congestive heart failure:
  - Failure to thrive, poor feeding, and diaphoresis
  - Increased respiratory work, chest wall retractions
  - Tachypnea, grunting, nasal flaring
  - Gallop rhythm
  - Hepatomegaly

Bedside monitoring data
- ECG tracing: rhythm other than normal sinus
- Arterial waveform: blunted upstroke and narrow pulse pressure
- Atrial pressure change: see Table 36.6
- Urine output:
  - <1.0 mL/kg/hour in neonates, infants, and children
  - <25 mL/hour in older patients

Laboratory and radiographic data
- SvO_2: decreased (<65–70%) with an increased (>30%) A-VO_2 difference
- Acid–base balance:
  - Metabolic acidosis with increased anion gap
  - Increased arterial lactate (>2.0 mmol/L)
- Electrolytes:
  - Hyperkalemia
  - Elevated BUN and Cr
  - Increased liver transaminases
- Chest radiography:
  - Cardiac enlargement
  - Abnormal (increased or decreased) pulmonary blood flow
  - Pulmonary edema

A-V, arteriovenous; BUN, blood urea nitrogen; Cr, creatinine; SvO_2, systemic venous oxygen saturation.

Surgical factors

Residual or unrecognized defects

A thorough understanding of the underlying cardiac anatomy, surgical findings, and surgical procedures is essential because this will direct the initial postoperative evaluation and examination. Residual lesions may be evident by auscultation, intracardiac pressures and waveforms, and oxygen saturation data. For example, a large V-wave on the left atrial waveform may indicate significant residual mitral valve regurgitation. An increase (step-up) of the right atrial-to-PA oxygen saturation of more than 10% may indicate a significant intracardiac shunt across a residual VSD [45].

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Table 36.6 Factors that should be considered when the measured atrial pressure is outside of the anticipated range

Increased atrial pressure
- Increased ventricular end-diastolic pressure
  - Decreased ventricular systolic or diastolic function
  - Myocardial ischemia
  - Ventricular hypertrophy
  - Ventricular outflow obstruction
  - Semilunar valve disease
- Mitral or tricuspid valve disease
- Large left-to-right anatomic shunt
  - Residual ventricular septal defect
  - Systemic-to-pulmonary artery connection
- Chamber hypoplasia
- Intravascular or ventricular volume overload
- Cardiac tamponade
- Dysrhythmia
  - Tachyarrhythmia
  - Complete heart block
- Artifactual
  - Catheter tip not in the atrium (e.g., in a ventricle, internal jugular vein, or wedged in pulmonary vein)
  - Pressure transducer below level of heart or improperly calibrated or zeroed
  - Concomitant drug infusions through the atrial line

Decreased atrial pressure
- Inadequate preload
- Artifactual
  - Catheter malfunction (e.g., cracked or clotted)
  - Pressure transducer above level of heart, or improperly calibrated or zeroed

However, if there are significant concerns for important residual lesions that are compromising CO and ventricular function, further evaluation with echocardiography and/or cardiac catheterization should be considered. Imaging of the heart may be difficult immediately after surgery because of limited transthoracic access and acoustic windows (e.g., due to chest tubes). During transthoracic echocardiography, it is important that hemodynamics are closely observed, because inadvertent pressure applied with the transducer may adversely affect filling pressures and mechanical ventilation. Similarly, vigorous antegrade flexion of a transesophageal echocardiography probe may induce pulmonary hypertension by altering left atrial filling due to partial obstruction of a mainstem bronchus.

Although surgery may be routine for many uncomplicated defects such as ASD closure, the approach for more complex intracardiac repairs may cause specific postoperative problems. For example, if a right ventriculotomy is performed to close the VSD in a patient with TOF, RV dyskinesia and poor contraction may be apparent. On the other hand, if a transatrial approach had been used to close the VSD in the same patient, the risk for atrioventricular valve injury or dysrhythmias, such as junctional ectopic tachycardia and heart block, is increased. Often unexpected findings or technical difficulties at the time of surgery mean that modifications to the approach or procedure are necessary. A difficult procedure may lead to a longer time on CPB or additional traction on cardiovascular structures.

Complications related to surgery

Failure of adequate hemostasis may expose the patient to significant volumes of transfused blood products, and if there is inadequate drainage via chest tubes placed at the time of surgery, the risk for cardiac tamponade is significant. This may be an acute event, but more commonly, it is evident by progressive hypotension with a narrowing pulse width, tachycardia, an increase in filling pressures, and reduced peripheral perfusion with possible evolving metabolic acidosis. A sudden decrease in chest tube drainage (e.g., caused by an obstructive clot) should raise the suspicion for the potential of tamponade. This is primarily a clinical diagnosis, and treatment (i.e., opening of the sternum and potential need for chest washout and/or clot removal) should not be delayed while waiting for echocardiographic confirmation.

Myocardial ischemia from inadequate coronary perfusion is often an under-appreciated event in the postoperative pediatric patient. Nevertheless, there are a number of circumstances in which ischemia may develop, compromising ventricular function and CO. Myocardial ischemia may occur intraoperatively because of problems with cardioplegia delivery or insufficient hypothermic myocardial protection, and from intracoronary air embolism. In the CICU setting, mechanical obstruction of the coronary circulation is usually the cause of myocardial ischemia rather than coronary vasospasm. Examples include extrinsic compression of a coronary artery by an outflow tract conduit, annulus of a prosthetic valve or chest tube, and kinking or distortion of a transferred coronary artery button. While electrocardiogram (ECG) changes may indicate ischemia (e.g., ST-segment abnormalities), a sudden increase in left atrial pressure or sudden onset of a dysrhythmia such as ventricular fibrillation or complete heart block may be an earlier warning sign.

Cardiopulmonary bypass and the systemic inflammatory response

The effects of prolonged CPB relate in part to the interactions of blood components with the extracorporeal circuit. This is magnified in children due to the large bypass circuit surface area and priming volume relative to patient blood volume. Humoral responses include activation of complement, kallikrein, eicosinoid, and fibrinolytic cascades; cellular responses include platelet activation and an inflammatory response, with an adhesion molecule cascade stimulating neutrophil activation and release of proteolytic and vasoactive substances [46–49].

The clinical consequences can include increased interstitial fluid, generalized capillary leak, and potential multiorgan dysfunction. Total lung water is increased with an associated decrease in lung compliance and increase in A-aO_2 gradient; some of these effects can be attenuated by hemofiltration or modified hemofiltration in the operating room (OR) [50, 51]. Myocardial edema results in impaired ventricular systolic and diastolic function. A secondary fall in CO by 20–30% is common in neonates in the first 6–12 hours following the arterial switch operation, contributing to decreased renal function and oliguria [52]. Sternal closure may need to be delayed due to mediastinal edema and associated cardiorespiratory compromise when closure is attempted. Ascites, hepatic congestion, and bowel edema may affect mechanical

ventilation as well as intestinal function (e.g., a prolonged ileus causing a delay in enteral feeding). A coagulopathy post-CPB may contribute to delayed hemostasis. The clinical manifestation of some of these issues may be attenuated with the lower priming volumes and higher hematocrits used on modern bypass circuits (see Chapter 12 for a detailed discussion of the inflammatory response to CPB).

Dysrhythmias

The ECG is an essential component of the initial postoperative evaluation because the CICU team must identify whether the patient is in sinus rhythm early in the recovery period. If the rhythm cannot be determined with certainty from a surface 12- or 15-lead ECG, temporary epicardial atrial pacing wires, if present, can be used with the limb leads to generate an atrial ECG [53]. Also, right and left atrial waveforms are useful in diagnosing atrioventricular synchrony (see Chapter 13). Temporary epicardial atrial and/or ventricular pacing wires are routinely placed in many patients to allow mechanical pacing if sinus node dysfunction or heart block should occur in the early postoperative period. Because atrial wires are applied directly to the atrial epicardium, the electrical signal generated by atrial depolarization is significantly larger and thus easy to distinguish compared with the P-wave on a surface ECG. Sinus tachycardia, which is common and often secondary to medications (e.g., sympathomimetics), pain and anxiety, or diminished ventricular function, must be distinguished from a supraventricular, ventricular, or junctional tachycardia. Any of these tachyarrhythmias can lower CO by either compromising diastolic filling of the ventricles or depressing their systolic function [54, 55]. High-grade second- and third-degree (or complete) heart block can diminish CO by producing either bradycardia or loss of atrioventricular synchrony or both. Third-degree block is transient in approximately one-third of cases. If it persists beyond postoperative days 9–10, it is unlikely to resolve, and a permanent pacemaker is indicated (see Chapter 22) [56].

Low preload

The diagnosis of insufficient preload is usually made by monitoring the mean atrial pressure or central venous pressure. The most common cause in the CICU is hypovolemia secondary to blood loss from postoperative bleeding. Initially after surgery and CPB, the filling pressures may be in the normal range or slightly elevated, but this often reflects a more centralized blood volume secondary to peripheral vasoconstriction and venoconstriction following hypothermic CPB. As the patient continues to rewarm and vasodilate in the CICU, additional intravascular volume may be necessary to maintain an adequate circulating blood volume and preload. There may also be significant third-space fluid loss in neonates and small infants who manifest the greatest systemic inflammatory response following CPB. The "leaking" of fluid from vessels into serous cavities (e.g., ascites) and the extracellular space (peripheral edema that can progress to anasarca) requires that these patients receive close monitoring and volume replacement to maintain an adequate circulating blood volume. Patients with a hypertrophied or poorly compliant ventricle, and those with lesions dependent on complete mixing at the atrial level, also often require additional preload in the early postoperative period.

High afterload

Elevated afterload in both the pulmonary and systemic circulations frequently follows surgery with CPB [52, 57]. Excessive afterload in the systemic circulation (elevated SVR) results in diminished CO and is typically manifest by decreased peripheral perfusion and cool extremities. Treatment of elevated SVR includes recognizing and improving conditions that exacerbate vasoconstriction (e.g., pain and hypothermia) and administering a vasodilating agent. A vasodilator, which can be a phosphodiesterase inhibitor (e.g., milrinone), a nitric oxide donor (e.g., nitroprusside), a calcium channel blocker (e.g., nicardipine), or a peripheral α-receptor antagonist (e.g., phenoxybenzamine or phentolamine), can be added to an inotropic agent such as epinephrine to augment CO. Neonates, who tolerate increased afterload less well than older infants and children, appear to derive particular benefit from afterload reduction therapy [58–60].

Decreased myocardial contractility

Because decreased myocardial contractility occurs frequently after reparative or palliative surgery with CPB, pharmacologic enhancement of contractility is used routinely in the CICU. Before initiating treatment with an inotrope, however, the patient's intravascular volume status, serum-ionized Ca^{2+} level, and cardiac rhythm should be considered. Inotropic agents enhance CO more effectively if preload is adequate, so IV colloid or crystalloid administration should be given if preload is low. If hypocalcemia (normal serum-ionized Ca^{2+} levels are 1.14–1.20 mmol/L) is detected, supplementation with IV calcium gluconate or calcium chloride is appropriate, because Ca^{2+} is a potent positive inotrope itself, particularly in neonates and young infants. Supranormal supplementation of calcium should be avoided, however, as increased levels of diastolic myocardial calcium are potentially cytotoxic [61].

Dopamine is often the first-line agent used to treat either mild hypotension (10–20% decrease in normal mean arterial blood pressure for age) or moderate hypotension (20–30% decrease in normal mean arterial blood pressure for age). This sympathomimetic agent promotes myocardial contractility by elevating intracellular Ca^{2+}, both via direct binding to myocyte β_1 adrenoceptors and by increasing norepinephrine levels. Dopamine is administered by a constant infusion because of its short half-life, and a usual starting dose for inotropy is 5 μg/kg/min. At a dose >5 μg/kg/min, dopamine should ideally be infused through a central venous catheter to avoid superficial tissue damage if extravasation were to occur. The dose is titrated to achieve the desired systemic blood pressure, although some patients, especially older children and adults, may develop an undesirable dose-dependent tachycardia. The challenge with dopamine is its simultaneous effects on β, α, and dopaminergic receptors, often resulting in undesired rhythm disturbances despite maintaining an adequate blood pressure [62]. For this reason, low-dose epinephrine, up to 0.05 μg/kg/min, is also a useful first-line inotropic agent, and it may have fewer

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arrhythmogenic side effects than dopamine in pediatric patients. If a patient does not respond adequately to dopamine up to 10 μg/kg/min or has severe hypotension (more than 30% decrease in mean arterial blood pressure for age), treatment with epinephrine should be considered.

Epinephrine may also be used as a first-line agent to treat mild-to-moderate hypotension. It should be given exclusively via a central venous catheter. A typical starting dose is 0.01–0.05 μg/kg/min with subsequent titration of the infusion to achieve the target systemic blood pressure. At high doses (i.e., ≥0.2 μg/kg/min), epinephrine can produce significant renal and peripheral vasoconstriction, tachycardia, and excessive myocardial oxygen demand (chronotropic and vasopressor effects) [58]. Patients with severe ventricular dysfunction who require persistent or escalating doses of epinephrine >0.15–0.2 μg/kg/min may benefit from opening of the sternum and/or should be evaluated for the possibility of mechanical circulatory support with a ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO).

Norepinephrine is a direct-acting α agonist that primarily causes arteriolar vasoconstriction, but it also has positive inotropic actions. At doses of 0.01–0.2 μg/kg/min, it can be considered in patients with severe hypotension and low SVR (e.g., "warm" or "distributive" shock), inadequate coronary artery perfusion, or inadequate pulmonary blood flow with a systemic-to-PA shunt. It is also useful in patients with preserved systemic ventricular function but failing or inadequate RV contractility (PVOD or postoperative TOF with restrictive RV physiology). In patients with normal hearts, variation in afterload is accommodated by varying stroke volumes and contractility; the normal heart works at peak efficiency and contractility exceeds afterload. This increased contractility is also transferred to the RV through the shared intraventricular septum. The increased afterload also improves the filling characteristics of the LV (by shifting of the interventricular septum) and augments RV coronary perfusion (especially in systemic RV pressure where the RV is now dependent exclusively on diastolic aortic root pressure for coronary perfusion). In the failing heart and in patients with limited ventricular reserve, an increase in afterload may not be matched by an increase in contractility, with a resultant fall in CO.

There can be a decrease in responsiveness to increasing doses of catecholamines over time; vasopressin at a dose of 0.1–0.5 mu/kg/min is a potent vasopressor that may help improve the hemodynamics in advanced shock without compromising cardiac function or other adverse sequelae [63].

A combination of epinephrine at lower doses (e.g., <0.1 μg/kg/min) or dopamine with an IV afterload reducing agent, such as milrinone, can help support patients with significant ventricular dysfunction accompanied by elevated afterload. Milrinone inhibits cyclic nucleotide phosphodiesterase III, thereby increasing cAMP, which results in an increased intracellular calcium concentration. In addition to acting as a positive inotrope, increased cAMP relaxes the systemic vasculature, leading to a decrease in afterload as well as a decrease in PVR [59]. The use of milrinone after neonatal and pediatric cardiac surgery has increased significantly over the past 15 years, in part due to the results of a double-blind, placebo-controlled multicenter trial that demonstrated a significant decrease in the incidence of LCOS (milrinone dose 0.75 mcg/kg/min) compared to placebo after infant and pediatric corrective heart surgery [42]. A more recent meta-analysis evaluating the use of prophylactic milrinone in children undergoing surgery for congenital heart disease found that while there is some evidence it may lower the risk for LCOS, there is currently insufficient evidence to conclude that milrinone helps prevent LCOS or mortality [64].

Patients who have the clinical features of relative adrenal insufficiency may benefit from stress steroid therapy [65, 66]. This is primarily a clinical finding of poor vascular tone with persistent hypotension and volume requirement that is refractory to increasing inotrope and/or vasopressor support. The serum cortisol level may be low or show a limited response to adrenocorticotropic hormone stimulation testing [67]; however, the ranges of normal have not been established for pediatric patients after cardiac surgery, in particular for newborns and infants. There is no consistent correlation between serum cortisol level and the incidence of LCOS; nevertheless, stress doses of hydrocortisone (50 mg/m^2/day) have been associated with increased systemic blood pressure and lower inotrope scores, although they have not been definitively demonstrated to improve eventual survival. A recent randomized controlled clinical trial also demonstrated that prophylactic, postoperative hydrocortisone infusion reduces the prevalence of LCOS after neonatal CPB [68]. The increased risk for infection and poor wound healing associated with stress dosing of steroids has led to a recommendation for shorter periods of administration (e.g., over 3–5 days) rather than continuing with a long taper [69].

Hypothyroidism is another cause for a persistent LCOS after cardiac surgery. Triiodothyronine (T_3) levels have been demonstrated to be low after CPB and may remain low for up to 5 days after surgery, particularly if a sick euthyroid state develops and there is decreased conversion of thyroxine (T_4) to the biologically active T_3 in peripheral tissues [70, 71]. A pediatric randomized controlled trial evaluating protocolized treatment with T_3 (two doses of 0.4 μg/kg during surgery and three doses of 0.2 μg/kg at 3, 6, and 9 hours after cross-clamp release) demonstrated improvements in ejection fraction and time to extubation, specifically in patients younger than 5 months [72].

Delayed sternal closure

Sternal closure following cardiac surgery can restrict cardiac function and also interfere with efficient mechanical ventilation. This is particularly important for neonates and infants, in whom considerable capillary leak and edema can develop following CPB, and in whom cardiopulmonary interactions have a significant impact on immediate postoperative recovery. In the OR, mediastinal edema, unstable hemodynamic conditions from both systolic and diastolic dysfunction, and ongoing bleeding are indications for delayed sternal closure, although it may also be considered semi-electively for patients in whom hemodynamic or respiratory instability is anticipated in the immediate postoperative period (e.g., following a modified Norwood procedure for HLHS). Urgent reopening of the sternum in the CICU following surgery is associated with higher mortality compared with leaving the sternum open in the OR [73], and successful sternal closure

can be achieved for most patients by postoperative day 4 with a low risk of surgical site infection [74]. Patients in whom this cannot be achieved and who have additional risk factors (e.g., neonate, need for ECMO, modified Norwood procedure) have an 11% superficial sternal infection (SSI) rate and significantly greater mortality [75]. Additional discussion of hemodynamic management is presented in Chapter 21.

KEY POINTS: MYOCARDIAL DYSFUNCTION AND HEMODYNAMIC MONITORING

- Low CO may be related to residual lesions, myocardial dysfunction, or a systemic inflammatory reaction related to bypass.
- LCOS may result from adverse effects on rhythm, preload, afterload, or myocardial contractility.
- Restoration of circulating volume and vasoactive agents are the first-line therapies. Corticosteroids and thyroid supplementation are the second-line adjuncts.

Cardiopulmonary resuscitation in the cardiac intensive care unit

Pediatric in-hospital cardiac arrest (IHCA) has been a rapidly evolving field of research over the past two decades. Compared to studies in the early 2000s, more recent results show that survival after pediatric IHCA has improved from ~15 to ~40%, largely highlighting an improvement in pediatric resuscitation care. Specifically, the factors contributing to this progress include the following: 1) clinical practice guidelines focused on vigilance and monitoring in the ICU setting, allowing for earlier recognition and prompt initiation of resuscitation efforts; 2) an increase in institutional and national quality improvement efforts surrounding resuscitation care; 3) a focus on cardiopulmonary resuscitation (CPR) quality metrics; and 4) the increased utility of extracorporeal-CPR (E-CPR) to achieve return of circulation [76]. Recognition of the high likelihood for cardiac arrest (CA) and need for CPR are among the primary reasons for creating specialized cardiac units (CICUs) and teams (e.g., ones led by pediatric cardiac intensivists). Although rates of CA remain higher in the CICU compared to the noncardiac pediatric ICU (PICU) population (3.1 vs. 1.8%) [77–79] and SC (those in the CICU following cardiac surgery) patients demonstrate higher rates of CA, they have improved outcomes compared to noncardiac groups. Furthermore, SC patients also have improved CA rates and outcomes when compared to MC (those in the CICU without preceding cardiac surgery) patients [78–80]. Improved outcomes in SC groups are believed to be related to the likelihood of more invasive monitoring in the postoperative CICU setting, younger age of SC groups at the time of arrest (greater age-related chest wall compliance allowing for better CPR quality), lower likelihood of preexisting conditions, noncardiac organ dysfunction, and an increased likelihood of E-CPR deployment during CPR [80, 81].

The ability to rescue a patient from a decompensation event is often used as a metric of unit, team, and system performance, and it requires the thorough exchange of information, high-quality monitoring and resuscitative measures, and specific resources immediately available to facilitate resuscitation such as E-CPR. However, perhaps a better metric may be the ability of a team to anticipate and/or recognize an evolving clinical picture of decompensation and prevent a critical event from occurring in the first place. Ongoing quality improvement initiatives among CICUs across the United States in recent years have facilitated improved outcomes after cardiac surgery in the CICU through data-sharing and collaborative learning models [82].

A CPR event often progresses through five phases. It is important to recognize the phase of care at any given moment, as a vital therapeutic action in one phase may be detrimental in a subsequent phase.

Prearrest phase: monitoring and event risk reduction

The first role of critical care teams is to identify patients at risk for decompensation and cohort them in the ICU where continuous anticipatory monitoring is possible. This is straightforward for most postoperative SC patients, but it becomes challenging for those patients who require interhospital transport or for those patients in the emergency department or hospital acute care units. A rapid response team (RRT) or medical emergency team (MET) that is based out of the ICU is a useful resource to allow transition of a critically ill child to the ICU prior to a CA [83–86]. Invasive (central venous and arterial blood pressure) hemodynamic monitoring combined with pulse oximetry and continuous ECG monitoring are the basics for any critically ill patient (medical or surgical). The importance of hemodynamic trends (e.g., progressive tachycardia and a narrowing pulse pressure) and frequent confirmation by physical examination cannot be overemphasized. A low invasive arterial blood pressure in a patient with poor central and peripheral pulses on clinical examination is likely to be real, and these findings should not be attributed to a technical problem with the monitoring system [87]. Additional monitoring by blood gas, lactate, and central venous oxygen sampling coupled with echocardiography allow static and dynamic trend assessments, which can support the impression provided by physical examination and basic monitoring [88–90]. NIRS does not rely on pulse detection, and it is thus useful in patients with a low CO state who are at increased risk for CA [91].

The use of capnography to monitor end-tidal CO_2 ($ETCO_2$) is especially valuable in patients with marginal CO or tenuous pulmonary blood flow dependent on an aortopulmonary shunt. Dramatic reductions (or loss) in $ETCO_2$ signals/tracings can be the first indicator of the prearrest state or critical shunt obstruction [87].

Although LCOS can often be managed preemptively using inotropic agents (see earlier sections), patients at risk for rapid deterioration often benefit from having low-dose IV boluses of either epinephrine (1 mcg/kg or 0.1 mL/kg of 1 : 100,000 solution) or phenylephrine (5 mcg/kg), followed by initiation of vasoactive infusions. Provision of these agents, which can be premixed and kept at the bedside for

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urgent administration per established indications, may rescue a patient with an acutely failing circulation and prevent a CA, thereby allowing time for other interventions such as sternal reopening or commencement of mechanical circulatory support before the need for CPR.

Formation of formal resuscitation teams with clearly defined leadership, structure, roles, and expectations with a focus on CPR quality metrics and compliance with CPR guidelines is an important prerequisite in any critical care environment. Frequent simulation of resuscitation events is another key component to prearrest and arrest performance [92–94].

Arrest phase: no-flow and low-flow states

The arrest phase consists of the "no-flow" phase of untreated CA and the "low-flow" phase during which CPR is initiated to achieve coronary and cerebral perfusion via administration of chest compressions and code-dose IV epinephrine (0.1 mg/kg of 1 : 10,000 solution) [95]. The goal is to recognize a loss of perfusing rhythm early in the event. Although the presence of an arterial pressure waveform and capnographic tracing can imply some amount of CO, the absence of palpable pulses is the *sine qua non* of CA. Uncertainty or vagueness with pulses should lead the team to err toward rapid, appropriate administration of CPR.

Maneuvers indicated in the arrest phase follow Pediatric Advanced Life Support (PALS) guidelines [96] that include, but are not limited to, the following: (i) securing an advanced airway (if not already present) while minimizing interruptions to chest compression [97]; (ii) provision of appropriate levels of supplemental oxygen; (iii) reducing over-ventilation to limit intrathoracic pressure increases and optimize cardiac preload during chest recoil; (iv) providing hard and fast cardiac compressions while allowing appropriate chest recoil, with the goal of maintaining diastolic blood pressure targets (if invasive blood pressure monitoring is already available) of 25 mmHg in infants and 30 mmHg in children over 1 year and an $ETCO_2$ of 20 [98]; (v) administering appropriate pharmacologic therapies, including early administration of code-dose epinephrine [99]; (vi) evaluating and intervening for inadequate lung (pneumothorax) or cardiac (tamponade) filling with needle thoracentesis and pericardiocentesis, respectively; and (vii) assessing for shockable rhythms early in resuscitation [100]. These therapies are continuously considered while assessing the response to interventions from objective monitoring (invasive arterial waveforms and quantitative $ETCO_2$) while minimizing interruptions in CPR.

There are unique differences compared to the PALS guidelines in the conduct of CPR in patients with specific types of CHD. This is particularly the case in patients with single ventricle physiology and a cavopulmonary connection. Sufficient time during chest recoil is needed to allow for pulmonary and cerebral blood flow. Even optimal closed-chest CPR results in cerebral blood flow that only approaches 25–30% of normal [101]. In children with pulmonary hypertension due to elevated PVR experiencing IHCA, ventilating with inhaled nitric oxide during CPR should be strongly considered to promote both forward flow/CO and gas exchange during resuscitation. Patients with significant atrioventricular valve regurgitation, semilunar valve regurgitation, outflow tract obstruction, and restrictive cardiac physiology may still not achieve adequate coronary and cerebral perfusion despite high-quality CPR [102, 103]. For patients in whom the likelihood of achieving high-quality CPR for specific cardiac lesions is low, and return of spontaneous circulation (ROSC) is not achieved early in resuscitation, early mobilization and deployment of E-CPR should be considered. Its use has been associated with improved outcomes when compared to conventional CPR in the CICU population [103–105]. Other advanced interventions, such as sternal reopening in SC patients early after sternotomy, also need to be considered. When mobilized early, open chest CPR can result in improved cerebral and coronary blood flows, and it has been associated with reasonable neurologic outcomes in survivors [106–108].

Postresuscitation phase: patient-focused care

After attaining hemodynamic stability, the goal of this phase is to optimize systemic oxygen and nutrient delivery (e.g., placing chest/pericardial drains; pacing the atria, ventricles, or both to achieve a desired heart rate and rhythm; optimizing vasoactive agents; replacing lost blood volume; and initiating mechanical support, if indicated) while minimizing systemic oxygen consumption requirements (e.g., adequate sedation, muscle relaxation, avoidance of hyperthermia). Based on the degree of global cerebral ischemic insult suspected, the institution of neuroprotective measures (such as normothermia, euglycemia, $PaCO_2$ goal of 35–40 mmHg, hypernatremia [serum Na > 140 mEq/L], appropriate cerebral perfusion pressures for age, seizure control, and electroencephalogram [EEG] monitoring) may be indicated to achieve the best possible neurologic outcome. Central nervous system (CNS) imaging (e.g., cranial ultrasound and brain CT and/or magnetic resonance imaging [MRI]) is typically performed and may assist in neurologic prognosis and further management postarrest [96, 109–111].

A vital part of this phase is to assess the cause for the arrest and initiate measures to prevent a recurrence. The event may have been predictable based on a difficult postoperative course and consideration given early for resuscitation with ECMO. In contrast, the event may have been unanticipated and further investigation is required, such as by a cardiac catheterization or return to the OR. It is important to discuss the appropriateness of potential interventions and, in some cases, to recognize situations that have become futile. These are not only appropriate discussions to have with relevant members of the medical/surgical team and subspecialty consultants, if involved, but also the child's parents/guardians [112–114].

Postresuscitation phase: team debriefing

Once a patient is stabilized and a care plan is devised and implemented, a postresuscitation team debriefing of the CA event is recommended in the resuscitation guidelines in order to improve future resuscitation team performance [103, 115]. This debriefing can be easy to overlook in a busy intensive care environment, but it is very important to include it as

part of the resuscitation effort. Its purposes are to provide feedback on areas for individual and team improvement for future events and to identify areas for quality improvement in an institution's resuscitation process. The ability to recognize any deficiencies, improve performance, and prevent future CAs is contingent on providing this systematic debriefing process with the team members in a safe and collegial environment [116–120]. Key aspects for broader dissemination (including process, personnel, and communication issues) should be documented (anonymously) in an effort aimed at continual performance improvement.

With the use of surveillance, team coaching through simulation, early detection of the prearrest state, establishment of rapid response services, optimizing team dynamics and performance during an arrest event, instituting mechanical circulatory support options early, if indicated, providing appropriate post-ROSC care, and performing periodic quality reviews of resuscitation events, a CICU can achieve improvements in rates/responses/outcomes of CA events. See Chapter 25 for additional detailed discussion of CA and resuscitation.

Management of postoperative complications

One of the most common features of the early postoperative course in the CICU is LCOS. Most often, the nadir of CO occurs at ~9–12 hours postoperatively, and it is precipitated by a mismatch in oxygen delivery and demand in the setting of post-bypass myocardial dysfunction, systemic inflammation, ischemia–reperfusion injury, electrolyte derangements, possible residual cardiac lesions, and derangements of the neurohormonal axis [121]. Therapies for LCOS generally involve inotropic agents, lusitropic agents, volume resuscitation, hydrocortisone administration, and minimizing oxygen demand while optimizing oxygen delivery [68, 122, 123]. Early postoperative bleeding can be another complication with varying etiologies related to preoperative and intraoperative factors; it requires close monitoring in the early postoperative period and replacement with blood products (e.g., packed red blood cells, fresh-frozen plasma, cryoprecipitate) if it exceeds designated threshold rates [124, 125]. Advanced procoagulant therapies (e.g., fibrinogen concentrate, anti-inhibitor coagulant complex, recombinant factor VII) and reopening of the sternum can also be considered after discussing the details with the cardiac surgeon and weighing the risks/benefits of procoagulant therapy for the patient's specific underlying cardiac anatomy/physiology (e.g., clotting risk can be increased with aortopulmonary shunts, cavopulmonary anastomoses). Chylothorax can also complicate the postoperative course and has been associated with specific traumatic and nontraumatic processes (e.g., single ventricle operations, aortic arch operations, Down/Noonan/Turner syndromes). If significant and prolonged, it may require lymphatic interventions to control [126–128]. Early postoperative arrhythmias, healthcare-associated infections, and central line-associated thromboses can also complicate the postoperative period [129–133]. All these postoperative complications can lead to prolonged mechanical ventilation days, ICU LOS, and increased postoperative morbidity and mortality. Such complications are often apparent early, but their impacts can be masked by expert management until de-escalations of support result in obvious clinical deterioration. Other common postoperative complications can affect the process of ventilator weaning or recovery to hospital discharge. Some of the more common postoperative complications seen in the CICU, their etiologies, and potential interventions are listed in Table 36.7.

The unanticipated postoperative course requires critical review. Based on the anatomical diagnosis, the preoperative risk profile, and the intraoperative course (technical performance of repair, any residual lesions of significance), one should be able to predict the major themes of the postoperative course. Recent data from the Residual Lesion Score (RLS) multicenter study of 1,250 infants undergoing surgery for TOF repair, complete atrioventricular septal defect repair, arterial switch operation for D-TGA, aortic arch/VSD repair, or the modified Norwood operation reported an incidence of RLS 3 (major residual lesions on echocardiography or residual lesion requiring reintervention before discharge) of 15–35% [134] (Figure 36.7). RLS 3 vs. 1 (no or trivial residual lesions) was a risk factor for fewer days alive and out of hospital ($p < 0.008$) and longer postoperative hospital stay ($p < 0.02$) for all operations. RLS 2 (minor residual lesions) was not consistently associated with outcomes. If the course is different than expected, it is incumbent on the CICU team to look actively for explanations. Initial evaluation of early postoperative complications may involve the use of ECG, echocardiography, ultrasonography, CT angiographic imaging, or cardiac MRI. However, more invasive evaluations such as cardiac catheterization can be required. Cardiac catheterization may be indicated to evaluate hemodynamics and obtain angiograms. These can guide decisions about the need for catheterization-based interventions or a return to the OR for surgery to address residual cardiac lesions. Recent studies support the safety and efficacy of early postoperative cardiac catheterization; low rates of complications are typical, and the results often guide changes in medical and/or surgical management when performed in the appropriate cohort of postoperative CICU patients [135–137]. Reopening of the sternum should also be considered for multiple etiologies: (i) to alleviate restrictive intrathoracic physiology from capillary leak syndrome, (ii) to alleviate cardiac tamponade, (iii) to improve pulmonary compliance and promote adequate gas exchange, and (iv) to prepare for initiation of mechanical circulatory support [138]. Patients with higher filling pressures, high vasoactive/inotropic support requirements, acute kidney injury (AKI) with worsening fluid balance, and higher early postoperative lactates have been identified in one study as at-risk groups that may require sternal reopening [138].

All pediatric cardiovascular programs, and specifically CICUs, should establish a process through which recognition and routine discussion of postoperative complications can occur. This allows identification of the patient who is not following an anticipated course and provides a forum for suggestions for evaluation and potential therapy. It also gives the care team an opportunity to review key themes from a quality perspective, ensuring critical attention to relevant processes for areas of improvement.

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Table 36.7 Postoperative Complications, Etiologies, and Interventions

Postoperative Complications	Etiologies	Intervention(s)
Low cardiac output syndrome	Myocardial dysfunction, systemic inflammation, ischemic-reperfusion injury	Inotrope/vasoconstrictor infusions, lusitropic agents, volume resuscitation, hydrocortisone, increasing DO_2, decreasing VO_2
Bleeding	Intra-op blood administration, inadequate intra-op hemostasis, dehiscence of suture lines, coagulopathy	Product administration (PRBCs, FFP, cryoprecipitate, fibrinogen concentrate, recombinant factors, anti-inhibitor coagulant complex), sternal reopening with exploration and source control
Arrhythmias	Junctional ectopic tachycardia (VSD patch closure) Complete heart block (damage to AV node) Supraventricular tachyarrhythmias (interventions on atria) Ventricular tachyarrhythmias (right ventriculotomy, coronary artery interventions, heart transplantation)	Temporary pacing wires (rapid atrial pacing, overdrive pacing, atrial or dual-chamber pacing) Antiarrhythmics (i.e. procainamide, amiodarone, lidocaine, esmolol) sedation, muscle relaxation, cooling, minimizing pro-arrhythmic pharmacologic therapies Electrophysiology study +/- ablation
Infections	Surgical site infection, central-line associated infection, ventilator-associated infection, sepsis, infective endocarditis, catheter-associated urinary tract infection	Targeted antibiotic therapy Imaging modalities to identify source (echocardiography, ultrasound, CT, MRI) Source control (removal of nidus of infection)
Chylothorax	Thoracic duct injury, abnormal lymphatic vasculature	NPO, antibiotics, fat-free diet, octreotide, methylprednisone, beta blockade, mTOR inhibitors, MEK inhibitors, magnetic resonance lymphangiogram, thoracic duct ligation, pleurodesis, pleuroperitoneal shunts
Central venous thrombosis	Central line placement, inadequate anticoagulation with foreign material in vascular structures, abnormal vascular anatomy	Anticoagulation, mechanical thrombectomy (surgical, catheterization), removal of intravascular catheters from vessel in question
Vocal cord injury	Intubation, recurrent laryngeal nerve injury	Bedside flexible bronchoscopy, therapies at discretion of otorhinolaryngology service
Diaphragm paralysis/paresis	Phrenic nerve injury	Evaluation with fluoroscopy or ultrasound (preferentially off invasive or noninvasive positive pressure ventilation), prolonged noninvasive positive pressure ventilation, diaphragmatic plication
Seizures	Intra-op ischemic insult, embolic stroke, intracranial hemorrhage	EEG, ultrasound or CT, anti-epileptic medications
Intestinal ischemia/ necrotizing enterocolitis	Limitation of cardiac output or systemic steal (i.e. single ventricle, shunt physiology, truncus, TGA), abnormal vascular pathology (i.e. mid-aortic syndrome, vasculopathy)	NPO, abdominal radiograph and ultrasound, pediatric general surgery consultation, optimizing DO_2, antibiotics
Sedation/analgesia withdrawal	Prolonged intubation and ICU length of stay, rapid weaning of pharmacologic therapies	Slow sedation drip weans, transitioning to enteral analgesic/anxiolytic/central alpha agonist therapies, monitoring withdrawal assessment tool (WAT) scores
Delirium	Sedation practices, related to intensive care stay	Environmental changes (restructuring sleep-wake cycles), melatonin, neuroleptic medications (risperidone, haloperidol), clustering bedside cares, monitoring of Cornell Assessment of Pediatric Delirium (CAP-D) scores
Feeding intolerance	Post-operative ileus, pre-operative intolerance of feeds, intestinal ischemia, reflux	Proton pump inhibitors, H_2-blockers, post-pyloric feeds, gut rest, assessment for adequate cardiac output, GI anatomic abnormalities assessment (i.e. malrotation, volvulus, intestinal strictures, Hirschsprung's)

DO_2 – oxygen delivery, VO_2 – oxygen demand, PRBC – packed red blood cells, FFP – fresh frozen plasma, VSD – ventricular septal defect, AV – atrioventricular, CT – computerized tomography, MRI – magnetic resonance imaging, NPO – *nil per os*, mTOR – mechanistic target of rapamycin, MEK – mitogen-activating protein kinase, EEG – electroencephalography, TGA – transposition of great arteries, ICU – intensive care unit, GI - gastrointestinal
Source: Gurpreet S. Dhillon

Patient safety and quality improvement in the cardiac intensive care unit

Vigilance and structured processes are vital to reduce or eliminate the risk of preventable harm. Critically ill patients require many decisions and processes to be efficiently delivered, and the environment is a key interface between human factors and technology. Although we are continually striving to improve the quality of care, every change in the system, despite capable team members and/or advanced technology, has the potential to adversely affect patient safety. The following general principles are fundamental to improving patient safety:

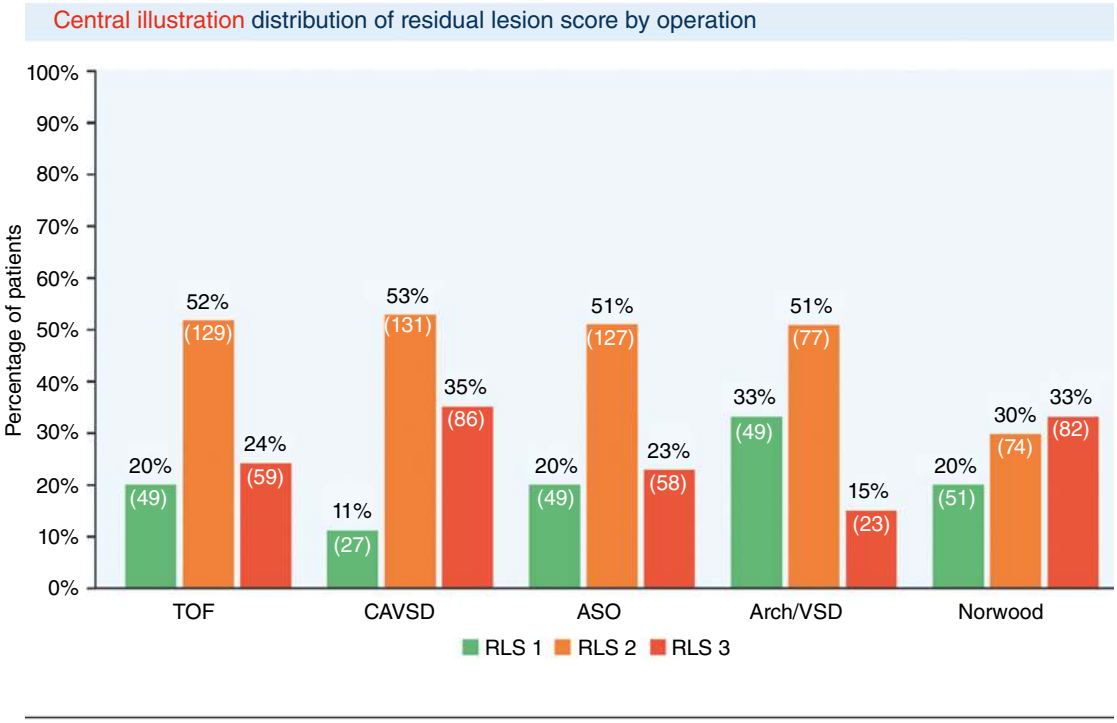


Figure 36.7 Residual lesion score figure. (Source: Nathan et al. [134]. Reproduced with permission of Elsevier.)

- Create a culture of transparency and respect.
- Measure performance continuously and provide timely data feedback to all team members in a relevant format.
- Insist on clear, direct, and closed-loop communication.
- Limit interruptions during focused activities as much as possible.
- Insist on systematic handovers during care transitions.
- Declare timeouts before invasive procedures.
- Ensure forced functions through appropriate human factor engineering of the environment (e.g., infusion pumps, alarm limits/silencing).
- Ensure read-backs and double checks when patient identification is key (blood products administration, transfer to OR).
- Create an anonymous, easy-to-use process for event reporting, review, and resolution.

Essential to any environment that values patient safety is a culture of accountability, openness, and teamwork. One must balance the value of creating a blame-free environment (essential for recognizing mistakes) with ownership of the mistake as a team (and as the intensivist). The latter is key to creating accountability that results in measurable change when needed. Accountability also requires prompt disclosure of significant error(s) to the patient's parents/guardian by the responsible attending intensivist. If these errors occurred outside the CICU (e.g., OR), the intensivist often plays a key role in facilitating disclosure by the appropriate individual(s).

Communication among care provider teams is paramount to safe patient care. Pertinent patient information sharing begins preoperatively, often with cardiac surgical case conferences, where the CICU team is a key stakeholder and participant. A structured, collaborative, and comprehensive transfer of care from the OR to intensive care team has been shown to be associated with fewer preventable complications [139]. Ensuring adequate time for handover, with minimal interruptions and use of structured communication tools, is essential.

Furthermore, there has been a concerted effort to improve postoperative care for all patients. In the adult population, the development and adoption of ERAS (Enhanced Recovery After Surgery) has been an international project to optimize patient outcomes and delivery of efficient care; nearly all surgical specialties are involved, including cardiac. The development of bundles and guidelines, audits, and team feedback has been a cornerstone of standardized, consistent care [140]. Data sharing and collaborative learning through multicenter initiatives such as the Pediatric Cardiac Critical Care Consortium (PC^4) have been organized to develop meaningful outcome analysis and benchmarking aimed at improving the care of complex pediatric cardiac surgical patients [82]. See Chapters 3 and 4 for further discussion of Quality and Outcomes, and Team Functioning.

Mechanical support of the circulation

Mechanical assist devices serve an important role in the care of children with critical myocardial failure, providing stable circulatory support for patients who have become refractory to aggressive medical management. Support may be required for only a short period, allowing for recovery from a self-limited process (e.g., acute viral myocarditis or postcardiotomy

myocardial failure), or it may be needed for long-term support to bridge a patient to cardiac transplantation. Historically, venoarterial (VA) ECMO has been the most common mode of mechanical support for patients in the CICU, and it continues to be a valuable tool secondary to its flexibility in cannulation strategy, ability to support both cardiac and pulmonary function, and ease of bedside deployment. Over the past decade, there has been a dramatic increase in the use of ventricular assist devices (VADs), as device manufacturers have begun to create miniaturized pumps that can reliably support pediatric patients [141]. The experience with the Berlin Heart EXCOR® VAD, in particular, has demonstrated that younger and smaller pediatric patients can be successfully bridged to heart transplant with results that are comparable with the adult VAD experience [142]. Despite improvements in device design and increased clinician experience with these devices, significant morbidity and mortality still occur in patients supported with mechanical assist devices, underscoring the need for further research to improve the care of this complex and high-risk patient population.

Extracorporeal membrane oxygenation

VA-ECMO is the most widely used mode of mechanical cardiopulmonary support for children with CHD. It fully supports heart and lung function similar to CPB and requires significant levels of systemic anticoagulation to maintain circuit performance. While VA-ECMO is the most commonly employed support strategy in CHD patients owing to its cardiac support, venovenous ECMO is occasionally utilized when cardiac patients with primary respiratory failure have preserved cardiac function. Figure 36.8 depicts a standard VA-ECMO circuit. Cannulation for VA-ECMO may be accomplished with venous drainage via the internal jugular vein, femoral vein, or centrally in the right atrium, while arterial input is via the carotid artery, femoral artery, or centrally in the aorta.

Over the past two decades, there has been a progressive increase in the use of ECMO for cardiac indications, as increasingly complex surgical interventions are being performed in younger patients. Currently, there are over 500 children/year, worldwide, who receive ECMO for cardiac support [143, 144]. The majority of these patients are placed on ECMO for postcardiotomy support, but other indications for ECMO include primary myocardial dysfunction secondary to cardiomyopathy or myocarditis, management of refractory arrhythmias, respiratory failure, refractory hypoxemia secondary to right-to-left intracardiac shunting, pulmonary hypertension, and for support during interventional cardiac catheterization or electrophysiology procedures in patients with unstable circulations. Overall survival to discharge is 40–65% in this heterogeneous group of patients, with certain subgroups demonstrating better outcomes [145–148]. Despite growing provider experience with ECMO, survival has remained largely unchanged over the past decade, although some centers report improving survival rates [149]. Further refinements in patient selection, timing of deployment, and creation of more biocompatible circuits are needed to increase successful outcomes.

ECMO has an important role in the resuscitation of critically ill patients following cardiac surgical intervention (i.e., postcardiotomy support). The best outcomes are seen in patients with a self-limited process, such as secondary myocardial failure post-CPB [150]. These patients typically demonstrate recovery of myocardial function within 48–72 hours, as evidenced by the return of pulsatility on invasive arterial blood pressure monitoring and improved systolic performance on echocardiography. VA-ECMO may also be an effective rescue therapy to bridge patients through correction of a reversible process, such as acute aortopulmonary shunt thrombosis [151]. In patients who do not follow this pattern, further investigation, such as a comprehensive echocardiogram and/or cardiac catheterization, should be undertaken to search for potential residual defects, as early identification and intervention may improve survival [152, 153]. Although not without potential hazard, cardiac catheterization can be safely undertaken in this high-acuity population [135, 154, 155]. The outcome of patients who require ECMO secondary to an inability to wean from CPB in the OR is particularly poor, with reported survival rates of only 10–30% [156, 157]. Despite isolated case reports describing myocardial recovery following prolonged periods of support, several studies in the postcardiotomy population have demonstrated that survival is <10% in ECMO runs longer than 10–12 days [158].

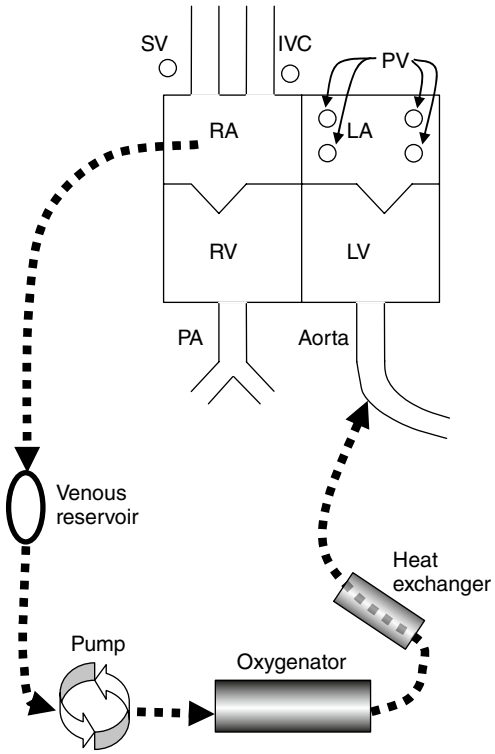


Figure 36.8 Extracorporeal membrane oxygenation (ECMO) circuit. The dashed lines represent flow through a venoarterial ECMO circuit. Blood is drained from the right atrium by direct atrial cannulation, or from an SVC catheter advanced into the right atrium. When using a roller pump, the blood is first drained to a small venous reservoir; with a centrifugal pump, a reservoir is not used. Blood then passes through a membrane oxygenator and heat exchanger before returning to the ascending aorta, which is cannulated directly or via the right carotid artery. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Support of the single ventricle patient can be problematic and merits further discussion. Outcomes in neonates with HLHS supported with ECMO following Norwood palliation are lower than other subpopulations, with hospital survival of 30% [159]. However, patients cannulated for severe hypoxemia, primarily caused by aortopulmonary shunt thrombosis, have better survival than patients supported for CA or myocardial failure [151]. Moreover, interstage mortality and progression to subsequent surgical palliations for infants who survive an ECMO course are comparable to infants not requiring ECMO after Norwood palliation [160]. Patients with systemic-to-PA shunts require unique management when supported by ECMO, as runoff through the shunt into the lung vessels will limit systemic blood flow and can lead to impaired end-organ perfusion. Strategies for managing this circulation include increasing ECMO flow into the range of 150–200 mL/kg/min to provide increased systemic output or to occlude the shunt partially to limit pulmonary runoff. Complete shunt occlusion is not recommended and has been associated with worse survival [161]. ECMO support in patients with a cavopulmonary connection has also been associated with poor outcomes. One case series reported 17% survival for patients with a bidirectional Glenn circulation and a strong association with severe neurologic injury [162]. Neurologic injury likely occurs because of the development of cerebral venous hypertension and impaired cerebral perfusion during low CO and/or CPR. That same case series report and a subsequent review of the Extracorporeal Life Support Organization (ELSO) registry for outcomes in Fontan patients revealed a 35% survival rate [162, 163]. Patients who demonstrated evidence of Fontan failure immediately after surgery had better outcomes compared with patients who required ECMO for progressive myocardial failure. Patients with a cavopulmonary connection may require the insertion of an additional venous cannula in the upper body to optimize venous drainage, particularly if a primary femoral cannulation strategy is instituted. A recent single-center review of 57 single ventricle patients (41 stage I palliation, 11 bidirectional Glenn, and 5 Fontan) reported that 53% were weaned off support, but only 33% survived to hospital discharge [164]. This outcome is consistent with broader data suggesting that the post-stage I circulation is a high-risk subset in which to apply support with a VAD.

ECMO support for patients with acute fulminant myocarditis is associated with the highest survival rates in children requiring ECMO for cardiac indications [165]. Survival rates of 60–80% are reported in this subpopulation [166]; these better results are likely attributable to the typically reversible nature of the myocardial dysfunction and the shorter periods needed to bridge to recovery. Myocardial recovery typically occurs within 2 weeks, and in those patients who continue to demonstrate severe myocardial dysfunction, conversion to a VAD for long-term support should be considered if cardiac transplantation is an option.

ECMO may also be used to bridge patients to cardiac transplantation, but its role in this indication has been usurped by VADs in the current era. Survival to transplant in patients utilizing ECMO as a bridge has been reported to be 40–60%, compared with 70–80% in patients bridged with VAD support [167, 168]. Given the limited number of available organs and relatively prolonged waiting list times, especially for the youngest patients, ECMO as a bridge strategy has major limitations in pediatric patients. Prolonged support with ECMO is associated with increasing complications, including bleeding, neurologic injury, end-organ failure, and sepsis.

Survival after pediatric IHCA is poor and reported to be 25–33% [169]. ECMO as part of CPR (i.e., E-CPR) is increasingly used as a procedure to rescue children who do not recover spontaneous circulation during standard CPR. Initiation of E-CPR is typically undertaken if there has been inadequate recovery with standard CPR following 10–15 minutes of resuscitation, provided there are no contraindications to mechanical support. Cannulation can be through either the chest, neck, or groin depending on the particular patient. A "clear" or asanguinous primed circuit allows for more rapid deployment, but some centers use banked O-negative blood that is stored within the CICU for rapid circuit priming. A review of the ELSO registry reported a 38% hospital survival rate for E-CPR, with patients who had an underlying cardiac diagnosis demonstrating more favorable outcomes [170]. There was no relationship between the type of cannulation strategy and survival. Interestingly, single-center reports of E-CPR outcomes demonstrate better survival, suggesting that the development of experienced teams with structured protocols can yield improved results [171]. Long-term neurologic outcome data are limited, but several studies report favorable neurologic outcomes in the majority of surviving patients [172–175]. Some patients, however, may develop significant neurocognitive morbidity [176].

A brief review of ECMO management principles follows. If time allows, blood is typically used to prime the ECMO circuit, but an asanguinous prime may be needed in the case of emergent deployment for E-CPR. Traditionally, perfusionists have primed the ECMO circuit, but many centers now have trained ECMO specialists (nurses, respiratory therapists, or physicians) who develop this skill set. Initially, the patient is supported with ECMO flows approaching full CPB flow (i.e., 100–150 mL/kg/min for patients in the range of 10 kg). This flow strategy allows for significant unloading of the myocardium and provides adequate perfusion to end organs to allow time for recovery. Inotropic agents are discontinued or minimized to decrease myocardial oxygen demand and to prevent downregulation of adrenergic receptors in the myocardium and peripheral vasculature. Vasodilator agents may be necessary to control systemic hypertension in order to prevent bleeding and cerebrovascular events. A left atrial vent may be required in those two-ventricle patients who have an intact/restrictive atrial septum and do not demonstrate any native systemic ventricular ejection, as left atrial hypertension, pulmonary edema, and subsequent pulmonary hemorrhage typically ensue [177, 178]. Ventilator support is adjusted to maintain FRC and minimize oxygen toxicity or barotrauma.

Anticoagulation is typically maintained with a heparin infusion beginning at 10–20 units/kg/hour, and it is titrated to maintain an activated clotting time (ACT) of 180–200 seconds. A lower ACT strategy may need to be utilized in recent postoperative patients with significant ongoing bleeding. More recently, some centers are using heparin activity levels to assist with their anticoagulation monitoring. A newer strategy is to use a bivalirudin infusion (a direct thrombin

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inhibitor) instead of heparin as the primary anticoagulant [179, 180]. Bleeding and coagulopathy are common, and blood products must be readily available for infusion into the circuit. The need for surgical exploration is also common, particularly among postcardiotomy patients, with prior sites of surgical intervention and the cannulation sites themselves being the most likely sources of bleeding. Typically, a goal platelet count >100,000, hematocrit >35%, and a prothrombin time within the normal range are maintained in these patients. Epsilon-aminocaproic acid (EACA) has been shown to be effective at reducing blood loss and transfusion in cardiac ECMO [181]. Recombinant factor VII has also demonstrated efficacy in reducing blood loss, but it can be associated with increasing thrombus burden in the circuit and thrombotic events [182]. Central nervous system (CNS) bleeding is a catastrophic complication and should be suspected whenever there is clinical and/or laboratory evidence of sudden decrease in hematocrit without another explanation for blood loss. Cranial ultrasonography is a commonly used screening tool among infants (via an open fontanelle) supported on ECMO. Portable CT for bedside brain imaging is a helpful tool to increase diagnostic yield, but it is not available in all hospitals.

Inadequate ECMO circuit volume is indicated by excessive negative pressure readings on the venous side of the circuit and an inability to maintain target flows and mean arterial pressures. Pre- and post-oxygenator pressures are monitored to assess both oxygenator function and distal resistance to flow. An increasing gradient between the pre- and post-oxygenator pressures in association with deteriorating gas exchange is an indication that oxygenator thrombosis has occurred. Increases in both pre- and post-oxygenator pressures indicate elevated distal resistance to flow secondary to mechanical issues with the arterial cannula or systemic hypertension.

Renal insufficiency and fluid overload can be managed by placement of a hemofilter in the circuit for continuous hemofiltration. If greater solute clearance is desired, hemodialysis can be run in tandem with the ECMO circuit. The development of acute renal failure while on ECMO has been associated with an increased risk for mortality [183, 184]. However, the use of continuous renal replacement therapy (CRRT) does not appear to confer risk for the development of chronic renal failure in the ECMO population [185, 186].

Infectious complications are prevented by meticulous sterile technique, and broad-spectrum antibiotics are initiated if sepsis is suspected. Sedation, analgesia, and, frequently, paralysis are required for these patients to optimize patient comfort and minimize risk for cannula site bleeding and disruption. Nutritional support is frequently delivered parentally while on ECMO, although enteral nutrition may be provided in the absence of splanchnic hypoperfusion.

ECMO support is weaned when the compromised myocardium has recovered, with the time course for recovery varying from as little as 24–48 hours to several weeks. Echocardiography (transthoracic, epicardial, or transesophageal) can be used to assess myocardial contractility both on full support and as support is weaned [187]. Before weaning flow, inotropic agents are typically restarted or increased, intravascular volume status is optimized, and ventilator support is increased. As ECMO flow is progressively reduced, additional titration of cardiovascular and ventilator support will be required with frequent assessments of clinical CO. If repeated attempts at weaning are unsuccessful, the team and the parents/guardians must decide if support should be withdrawn or if further pursuit of long-term mechanical support (i.e., a VAD) and cardiac transplantation is appropriate.

Ventricular assist devices

The application of VAD technology has increased dramatically in the pediatric population over the past decade [188]. Historically, VAD use was uncommon in children because of technical limitations, including device size and increased risk of device thrombosis secondary to use of flows that were outside the typical device operating range (lower due to smaller patient size). Short-term devices were primarily used; these devices required patients to be sedated and supported with mechanical ventilation, limiting opportunities for rehabilitation. Currently, short-term VAD support is most often used in postcardiotomy patients with an ischemic myocardium secondary to an anomalous left coronary artery from the pulmonary artery (ALCAPA), patients with late repair of D-TGA and an intact ventricular septum who develop LV failure following arterial switch, or for temporary support of RV failure following orthotopic heart transplantation or left ventricular assist device (LVAD) implantation [189].

With the arrival of the Berlin Heart EXCOR pump and the creation of miniaturized continuous flow devices, smaller pediatric patients can now be supported for longer periods and successfully bridged to cardiac transplantation. Long-term VAD support can be divided into paracorporeal pneumatic devices, such as the Berlin Heart EXCOR, or intracorporeal continuous flow devices, such as the HeartWare HVAD® and HeartMate III®. Given the compact design of the HVAD, it has become the most widely used continuous flow VAD in children. The HVAD is most commonly implanted in children with cardiomyopathy, but it has also been used with some success in children with CHD, including those with single ventricle physiology [190–192]. A recent study from ACTION, a collaborative pediatric VAD quality improvement network, demonstrates promising results related to HVAD use in children, with a 96% survival rate at 1 year and only 4% occurrence of stroke [193]. As of June 2021, the HVAD device was removed from the market after the U.S. Food and Drug Administration (FDA) advised healthcare providers to stop implanting the device due to a higher frequency of neurological events and patient deaths compared to other devices [194]. The SynCardia Total Artificial Heart® is an intracorporeal pneumatic device that provides biventricular support, but its use has been limited to larger adolescents secondary to its larger size. The Berlin Heart EXCOR VAD is the only one of these devices that has been specifically designed for a pediatric application and can support infants. There have been ongoing efforts as part of the National Institutes of Health-sponsored PumpKIN Program to create a durable continuous flow VAD that can support infants and small children. The Jarvik 2015 is the only remaining device from this program, signifying the challenges in creating pediatric-specific devices [195]. Unlike the previously described short-term VADs, children with these devices can be weaned off sedation, extubated, and

ambulate, allowing for pretransplant rehabilitation. Larger patients whose BSA permits implantation of the intracorporeal continuous flow devices can be discharged from the hospital following intensive training in the daily maintenance of their device.

Despite relatively recent introduction into practice in the United States over the past decade, a large body of experience has developed with the Berlin Heart EXCOR device. As compared with ECMO, patients can be supported for longer periods and more successfully bridged to transplant. The Berlin Heart investigational device exemption (IDE) trial reported that 88–92% of patients (two patient groups based on BSA) were successfully bridged to transplant or recovery [142]. Serious adverse events, including bleeding, infection, and stroke, occurred in 29% of the patients. A follow-up investigation examining all patients implanted with the Berlin Heart during the same study period as the IDE trial reported 75% survival to transplant or recovery [196]. Neurologic dysfunction occurred in 29% of the patients and was the leading cause of death. However, more recent data suggest that the incidence of stroke is decreasing [197]. Smaller patient size, end-organ dysfunction preimplantation, and biventricular support were all associated with increased risk of death while on VAD support. These findings underscore the importance of careful patient selection and timing of implantation.

Small infants and children with single ventricle physiology remain particularly problematic patient populations to support with VADs [191]. Smaller patient size, in particular those weighing <5 kg, was identified as an important risk factor for mortality in the Berlin Heart EXCOR bridge to heart transplantation study [196]. Whether this risk is related to patient-specific factors, such as immature hematologic function, or device-related issues remains unclear. Recognizing the difficulties related to supporting small infants with pulsatile devices, some groups have advocated for the use of short-term continuous flow devices such as the PediMag™ [198]. While survival with a VAD following Fontan palliation can reach 95%, survival after stage 1 and stage 2 procedures is much lower (30 and 40%, respectively). Success of VAD therapy in single ventricle patients is much lower compared to non-CHD patients, with higher mortality and a lower rate of effective bridge to transplantation [199]. For stage 1 and/or shunted patients, the need to support both the systemic and pulmonary circulations (i.e., two COs with one device) presents a unique challenge. If unable to achieve adequate decompression, the systemic venous and intracardiac pressures may increase as well as the amount of atrioventricular valve regurgitation.

Another important concept is the need to limit pulmonary blood flow in some manner, in order to decrease the risk of steal from the systemic circulation. For patients with Glenn physiology, VAD cannulation strategy is systemic ventricle (or atrial if the RV is heavily trabeculated) to ascending aorta. While the failing ventricle is volume unloaded compared to shunted physiology, the VAD may also need to support collateral circulation. Additional considerations include ensuring adequate intracardiac decompression to prevent failure of the Glenn circulation with development of a low-flow state in the systemic venous and pulmonary circuits. Continuous flow devices may better support this physiology; however, patient size is a major limitation in using an intracorporeal continuous flow device unless the patient is an older, school-aged child. Patient selection for VAD placement in failing Fontan physiology is important. Fontan patients with elevated ventricular filling pressures may be the better candidates compared to those with progressive end-organ injury and/or those with Fontan failure related to protein losing enteropathy or plastic bronchitis.

A brief discussion of VAD management follows, but a more in-depth review can be found in Chapter 37. For the pneumatic devices, stroke volume is fixed and thus output is adjusted by titrating the beat rate of the device to provide an adequate clinical CO and blood pressure. In continuous flow devices, the pump speed is titrated to achieve goal clinical CO and mean arterial pressure. Intravascular volume status and device filling can be monitored via central venous pressure and direct inspection for the paracorporeal devices, or via device parameters in the intracorporeal devices. Systemic anticoagulation is necessary to prevent device thrombosis, but at a lower level than that required for ECMO. Patients are initially treated with heparin infusions and then transitioned to low-molecular-weight heparin or warfarin once they have recovered from device implantation and achieved stable VAD settings. Platelet inhibition with aspirin, dipyridamole, and/or clopidigrel may also be required to prevent thrombus formation, usually based on the manufacturer's recommendations. For patients receiving LVAD support alone, medical support for the RV is critical for optimizing postimplant care. Inotropic support and inhaled nitric oxide for RV afterload reduction are helpful adjuvants to assist with RV function. If the RV is unresponsive to medical therapy, mechanical RV support may be necessary with either a short-term or long-term device. This decision is frequently made either in the OR during LVAD implantation or within the first postoperative hours in the CICU.

KEY POINTS: MECHANICAL SUPPORT OF THE CIRCULATION

- ECMO is the most common mode of mechanical cardiac support utilized in the CICU secondary to its flexibility in cannulation strategy, ability to support both cardiac and pulmonary function, and ease of deployment.
- ECMO is most effective in patients with myocarditis, reversible postcardiotomy myocardial failure, or shunt thrombosis. Prolonged support with ECMO is associated with increasing complications, including bleeding, neurologic injury, end-organ failure, and sepsis.
- ECMO may be used as an adjunct to assist with resuscitation of patients who do not recover spontaneous circulation during standard CPR. Long-term neurologic outcome data are lacking for this high-risk patient group.
- Increasing experience with VAD use has improved the care of patients with terminal heart failure who are awaiting cardiac transplantation. Patient selection and timing of device implantation are critical in optimizing patient outcomes.

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Hemostasis

The risk of postoperative bleeding in the pediatric cardiac surgical patient is multifactorial. Delayed hemostasis can be partly related to the deleterious inflammatory and hematologic effects of CPB, which include hemodilution from the bypass circuit prime, stimulation of the intrinsic coagulation pathway resulting in coagulation factor consumption, and platelet activation and aggregation leading to platelet loss and dysfunction [200]. Priming the bypass circuit with reconstituted whole blood has been demonstrated to be beneficial in neonates and infants undergoing cardiac surgery to reduce post-bypass bleeding [201]. Patient-specific factors identified as risks for postoperative bleeding include low CO with tissue hypoperfusion and associated disseminated intravascular coagulopathy, hepatic immaturity or dysfunction, the preoperative use of anticoagulants and antiplatelet agents, a history of prior cardiac surgery, the presence of extensive suture lines, and chronic cyanosis.

Prompt identification and control of surgical bleeding are essential in preventing the complications associated with massive transfusion. Categories of postoperative bleeding by volume and management strategies are listed in Table 36.8. Transfusion of platelets, plasma, cryoprecipitate, and/or fibrinogen concentrate to correct coagulopathy is an important initial intervention. In critically ill children with hemorrhagic shock, consensus guidelines suggest product ratios of 2 : 1 : 1 to 1 : 1 : 1 of red cells, plasma, and platelets, respectively, until the bleeding is no longer life-threatening [202]. Normalization of body temperature and correction of hypocalcemia can be helpful adjuncts in achieving hemostasis. Evidence of a prolonged partial thromboplastin time (PTT) with a normal heparinase-treated sample suggests the presence of residual heparin and can be corrected with an additional dose of protamine. Antifibrinolytic agents such as EACA and tranexamic acid (TXA) are used intraoperatively to reduce bleeding, but may also be effective in the CICU if coagulopathy and fibrinolysis persist [203]. These agents bind to plasminogen, rendering it incapable of binding to lysine residues on fibrin and thus inhibiting plasmin generation.

Table 36.8 Volumetric approach to postoperative bleeding

Evaluation	Laboratory assessment • INR, PTT, platelet count • Consider ACT, PTT with heparinase, TEG, ROTEM. Measure chest tube output
Chest tube output	Considerations
<5 mL/kg/hour	Review labs Monitor, usually resolves spontaneously
5–10 mL/kg/hour	Review labs Blood product replacement Volume resuscitation Consider protamine if residual heparin effect found on lab testing
>10 mL/kg/hour	Prompt communication with surgeons Consider chest re-exploration Review labs Ongoing blood product and volume replacement

INR – international normalized ratio, PTT – partial thromboplastin time, ACT – activated clotting time, TEG – thromboelastogram, ROTEM – rotational thromboelastometry

Critically ill children with heart disease are at risk for both bleeding and thrombosis [204]. Goal-directed therapy with factor concentrates has been used successfully in adult cardiac surgery patients, but data in children are limited [205]. Fibrinogen concentrate has been shown to be equivalent to cryoprecipitate in children undergoing cardiac surgery [206]. Off-label use of recombinant activated factor VII (rFVIIa) as a rescue agent for cases of refractory postoperative bleeding has been employed. However, recent studies have demonstrated that high-dose rFVIIa (>90 mcg/kg) is associated with significant thrombotic complications [207, 208]. The use of prothrombin factor concentrates (PCCs) in pediatric cardiac surgical patients has also gained interest. Similar to rVIIa, limited data for pediatric patients exist, and the thrombotic risk remains an issue [209, 210].

Irrespective of management strategies, post-bypass bleeding increases the risk of adverse outcomes such as need for postoperative dialysis and ECMO, and in-hospital mortality, especially in neonates [211]. Ongoing research with high-quality studies and comparable outcomes, focusing on monitoring tests, pharmacologic treatments, and development of clinical practice guidelines, are needed. Chapter 16 has an extensive presentation of bleeding and hemostasis in CHD surgery.

KEY POINTS: HEMOSTASIS

- Patients in the CICU are at risk for bleeding complications from exposure to inflammatory and hematologic effects of bypass, the presence of end-organ dysfunction related to LCOS, and the use of anticoagulants/antiplatelet agents.
- Postoperative bleeding associated with chest tube output of 5–10 mL/kg/hour requires aggressive medical management with blood product replacement and correction of coagulopathy. Output > 10 mL/kg/hour may require chest re-exploration.
- Adjuvant agents, such as EACA or TXA, rVIIa, and PCC, may be helpful in controlling postoperative bleeding, but their use can be associated with thrombotic events. Careful risk–benefit assessment must be done prior to use.

Infection control

Hospital-acquired infections are an important source of morbidity and mortality in ICUs, and they cause increased healthcare expenditure [212, 213]. Patients in CICUs are particularly vulnerable secondary to the high incidence of surgical procedures, exposure to the inflammatory and immunomodulatory effects of CPB, and the routine use of invasive devices. Bloodstream infection and surgical site infection (SSI) are the most common, followed by ventilator-associated pneumonia and urinary tract infection [214, 215].

Studies examining risk factors for nosocomial infection frequently identify younger age, higher disease complexity (e.g., based on RACHS-1 and PRISM scores), and the presence of delayed sternal closure as factors that convey increased risk [214–216]. An analysis of central line-associated bloodstream infection (CLABSI) in the PC[4] collaborative demonstrated a 70% prevalence of central line use in almost 20,000 admissions [133]. The median duration of use was 4 days, and there was a 2% incidence of central line-associated thrombosis and a 1% incidence of CLABSI with medical admissions; younger age, greater surgical complexity, and greater number of catheter days were risk factors for both. Table 36.9 lists factors associated with CLABSIs in cardiac surgical patients.

Reviews of SSIs identify younger age, inappropriate timing of prophylactic antibiotics, excessive bleeding in the immediate postoperative period, and prolonged CPB as important risk factors [217, 218]. In the setting of delayed sternal closure, multiple episodes of delayed sternal closure and ECMO use have been identified as independent risk factors for SSI [75].

Efforts at limiting the occurrence of nosocomial infection have focused on staff education, good hand hygiene, creation of central line insertion and maintenance bundles, daily evaluations of the need for all indwelling devices (e.g., central venous line, Foley catheter, ETT), and regular audits of staff compliance. When trialed, these maneuvers have proved successful and led to decreasing rates of infection [219]. In addition, quality improvement projects following the PLAN-ACT-STUDY-DO model have proven highly effective in reducing nosocomial infections [220]. Maneuvers to minimize SSI have included a preoperative chlorhexidine bath prior to the day of surgery, standardizing intraoperative skin preparation and antibiotic timing, standardization of dressing care, early removal of pacing wires, and utilization of sterile technique for transthoracic echocardiograms in fresh postoperative patients [217]. Given the previously identified risks of steroid use and exposure to blood products, future studies may investigate the efficacy of limiting these interventions in CICU patients.

Table 36.9 Factors associated with an increased risk for catheter-associated bloodstream infection in patients with congenital cardiac defects before and after surgery

- Younger age
- Higher STAT category
- Total catheter days
- Multiple catheters in place
- History of cardiac catheter intervention
- Cardiac arrest
- Use of mechanical circulatory support
- Chylothorax
- Prior infection
- Open chest
- Unplanned reintervention
- History of thrombosis

STAT, Society for Thoracic Surgeons-European Association for Cardiothoracic Surgery mortality score.

Neurologic monitoring/assessment and complications

Surgical mortality for patients with CHD has progressively declined over the past several decades, yielding a growing population of survivors who display an incidence of neurologic, developmental, and psychiatric disabilities that are notably greater than normal healthy children [221]. In particular, children who undergo repair or palliative procedures as neonates and infants appear to be the group at greatest risk [222]. These emerging data reinforce the importance of further refining preoperative, intraoperative, and postoperative care to minimize potential neurologic insults to the developing brain.

Historically, children with CHD but no identified associated genetic disorder were believed to have normal brain development. This precept has been challenged over the past decade with new studies utilizing advancements in MRI technology. MRI studies have demonstrated the presence of brain immaturity and white matter abnormalities prior to any surgical intervention [223]. These findings have been documented most consistently in patients with D-TGA and severe LV outflow obstruction, particularly HLHS and its variants [224]. Changes in fetal circulation secondary to the presence of these congenital heart lesions may contribute to these abnormalities, although future research is necessary to confirm causality [225]. In addition, fetal cardiac and brain development are linked, so genetic abnormalities that lead to CHD may also cause abnormal brain development [226, 227].

Although patients with CHD may have coexisting CNS abnormalities, they are also at risk of acquired neurologic injury throughout the perioperative period. These injuries may occur due to periods of hypoxia/ischemia, CNS hemorrhage, and embolic phenomenon. Premature infants are at additional risk for intraventricular hemorrhage. Older patients, particularly those with chronic cyanosis, are at risk for injury secondary to cerebral abscess and stroke, the latter related to venous or arterial thrombosis from erythrocytosis. In light of data illustrating the presence of preexisting brain injury, attempts to mitigate damage related to these perioperative insults take on even greater importance.

A large body of research over several decades has contributed to advances in intraoperative management with the goal of decreasing brain injury related to bypass, circulatory arrest, and surgery. These include the application of deep hypothermia to minimize injury during periods of ischemia/circulatory arrest, controlling the rate of body cooling and rewarming, optimizing perfusion pressure and flow via bypass, minimizing periods of circulatory arrest or avoiding it altogether with regional brain perfusion, optimizing hematocrit, adjusting pH and $PaCO_2$ during periods of hypothermia (pH stat strategy), and refining bypass circuit technology to minimize the risk for particulate or air emboli [228–230]. Choreoathetosis is historically a complication that could develop following cardiac surgery in children, particularly in older infants. Contributing factors to its development include inadequate brain cooling, rapid rate of cooling, α-stat blood gas strategy during cooling, and the presence of systemic-to-PA collateral vessels [231, 232]. Fortunately, this potentially devastating complication is uncommon in the current

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era where antegrade cerebral perfusion has become a more standard practice. In addition, intraoperative monitoring with NIRS to assess regional cerebral oxygen saturation has assisted in avoiding prolonged episodes of hypoxia/ischemia, particularly during periods of circulatory arrest or regional cerebral perfusion [233]. Some centers may also use transcranial Doppler assessment during regional perfusion to assess adequacy of bypass flow [234, 235].

Postoperative monitoring and care in the CICU also contribute to the avoidance of neurologic insults. Postoperative factors contributing to neurologic injury are related mainly to the development of persistent LCOS with depressed cerebral perfusion and potential progression to cardiovascular collapse. Assessment of CNS function may prove difficult, particularly in patients receiving sedation and/or neuromuscular blockade. The extension of the intraoperative practice of monitoring cerebral oximetry via NIRS to the CICU has allowed for a further portal into assessing the interplay between hemodynamics and the CNS. Several studies have demonstrated that sustained periods with low postoperative cerebral oxygen saturation (below a range of 45–55% by oximetry) are associated with poor outcomes, particularly in the HLHS population [236–238]. Some institutions have instituted protocols to alert providers when these threshold values are reached; interventions are then initiated, such as volume resuscitation, increased inotropy, modulation of afterload/vascular resistance, and increased sedation to minimize oxygen demand [239]. Further studies are needed to validate the efficacy of these protocols. Additional factors in patient management may play an important role in avoiding neurologic injury, including minimizing hyperventilation (to prevent reduction in cerebral blood flow) and avoiding hyperthermia. Post-bypass hyperthermia may develop from low CO with associated peripheral vasoconstriction or from aggressive rewarming practices. The avoidance of hyperthermia following pediatric traumatic brain injury is important, as early hyperthermia is associated with worse neurologic status [240]. Data from a neonatal porcine model of circulatory arrest also demonstrated the detrimental effect of hyperthermia on neurologic outcome [241]. Avoidance of hyperthermia in the postoperative period may help attenuate neurologic injury associated with circulatory arrest and periods of low output in the CICU [242]. The use of therapeutic hypothermia has been implemented to positive effect in neonatal hypoxic–ischemic brain injury and in adults following witnessed CA due to ventricular fibrillation [243, 244]. Its use has been extended to pediatric patients following CA, but there is currently no clear evidence demonstrating its benefit [245]. A recent randomized controlled clinical trial also did not demonstrate survival benefit of therapeutic hypothermia as compared to normothermia after pediatric IHCA [109]. Postarrest therapeutic hypothermia in patients with CHD may decrease the incidence of seizures, but it did not show additional benefits [246].

Historically, seizures were the most frequently observed neurologic complication following deep hypothermic circulatory arrest (DHCA), with a reported incidence of 4–25% [247]. Both focal and generalized seizures have been described, usually occurring on the first or second postoperative day. Status epilepticus was uncommon, and the occurrence of postoperative seizures did not increase the risk for seizures later in life. Because epilepsy rarely developed, these limited postoperative seizures were initially not thought to be of significant concern. However, the Boston Circulatory Arrest Study demonstrated that early postoperative seizures are a marker for worse neurodevelopmental outcome [248]. In recent years, postoperative seizures have become an uncommon event, with an incidence of 4%; the reduced incidence is likely secondary to improved techniques for neurologic protection as described earlier [249]. Other potential inciting events for postoperative seizures include embolic phenomenon and CA with development of severe hypoxic–ischemic injury. As stated previously, clinical detection of seizures in the CICU can be impaired by the presence of sedation and paralysis, necessitating careful assessment of autonomic manifestations such as sudden onset of tachycardia, hypertension, and pupillary dilation, although the cause of these signs can be difficult to distinguish from other hemodynamic causes. Acute declines in cerebral oximetry may also be noted, but as this technique assesses regional oxygen saturation, it may not reliably detect seizure activity in areas distant from the frontal cortex. EEG monitoring is a useful adjunct in the diagnosis of seizures; in particular, 24-hour video EEG monitoring can be helpful in assessing subtle or clinically-silent seizure activity (nonconvulsive status epilepticus) [250]. Imaging with head CT and/or MRI may be helpful, particularly if the seizures are focal in nature, suggesting the presence of a localized lesion such as an intracerebral hemorrhage or infarct. Treatment of postoperative seizures includes first-line IV administration of a benzodiazepine, typically lorazepam, followed by IV administration of fosphenytoin for persistent seizure activity [251]. Additional agents, including phenobarbital, levetiracetam, and a continuous midazolam infusion, may also be employed for refractory status epilepticus.

Stroke is another neurologic complication seen in the CICU. Awareness of this clinical entity has been heightened, as mechanical support with VADs has become the standard of care for most patients with end-stage heart failure. Other potential risk factors for stroke include the presence of intracardiac thrombus in association with ventricular dysfunction and arrhythmia, right-to-left intracardiac shunt, chronic cyanosis with associated erythrocytosis, mechanical valves, anticoagulant/antiplatelet use, and inherited or acquired thrombophilia [200]. A thorough history and physical examination are important to establish timing of the event, potential contributing risk factors, and the nature/severity of the neurologic deficits. Parents are often astute observers of subtle changes in their children, and their insights should be elicited. Initial signs and symptoms are age-dependent, with infants less than 6 months of age typically demonstrating nonspecific signs such as altered mental status (persistent irritability or depressed level of consciousness) and seizures. Older children may display focal neurologic findings, such as hemiparesis, which are associated with specific vascular territories in the brain. Cerebral venous thrombosis typically yields nonspecific findings across all age groups, with depressed mental status, headache, vomiting, and seizures being typical manifestations. Subsequent management includes neurodiagnostic imaging with head CT and brain MRI to assess for hemorrhage (CT) or focal areas of

ischemia/infarction. Cerebrovascular imaging may add further diagnostic information. Treatment involves efforts to restore or optimize perfusion to affected areas, modify risk factors, if possible, and deliver additional supportive care (e.g., institute mechanical ventilation if the airway cannot be protected and maintain appropriate cerebral perfusion pressure). The use of thrombolytics and anticoagulation is guided by a careful analysis of the risk–benefit ratio of these therapies, including risk for hemorrhage into a recently infarcted area.

Delirium, defined as an acute and fluctuating state of neurologic dysfunction, is becoming an increasingly recognized and important issue in the CICU patient population [252, 253]. Recent studies suggest a high prevalence of delirium in pediatric CICU patients, anywhere from 50 to 65%, with the majority in the postcardiotomy subpopulation [252, 254, 255]. Currently identified risk factors for development of delirium in the pediatric CICU population include the following: younger age (less than 2 years), developmental delay, higher severity of illness, longer CPB time, cyanotic disease, poor nutritional status, mechanical ventilation, and benzodiazepine use. Importantly, delirium has been found to be an independent predictor of prolonged CICU LOS. Delirium has also been shown to be an independent predictor of pediatric in-hospital mortality [256]. Given that delirium may contribute to increased ICU LOS, as well as possible as yet unrecognized long-term morbidities and mortality, screening is of utmost importance so that the CICU team can address modifiable risk factors and consider institution of pharmacologic treatment.

There are three main types of delirium: hypoactive, hyperactive, and mixed. Clinical guidelines recommend screening for delirium at least once a nursing shift [257]. There are two validated screening tools for pediatric delirium: the Pediatric and Preschool Confusion Assessment Method for the ICU (pCAM-ICU, psCAM-ICU) [258, 259] and the Cornell Assessment of Pediatric Delirium (CAPD) [260]. If a patient screens positive for delirium, the first steps should be to assess for underlying medical causes (e.g., infection, hypoxia, metabolic derangement, new neurologic insult), minimize iatrogenic risk factors (e.g., choice of sedative medications, use of restraints), and optimize the ICU environment (e.g., promote circadian rhythm, allow for soothing techniques and familiar items from the home environment, encourage family involvement at the bedside). If these interventions are not sufficient, then pharmacologic intervention, typically in the form of an atypical antipsychotic, may be considered. However, data on the use and efficacy of antipsychotics for pediatric delirium are lacking, and many centers appropriately consult a pediatric psychiatry team to help with medication management. A retrospective study found that the use of an atypical antipsychotic (quetiapine) in PICU patients was safe [261]. If an atypical antipsychotic is used, the QTc interval should be monitored closely, especially if the patient is receiving other QTc-prolonging medications.

A brief discussion about the potential impact of analgesia and sedative medication on brain development follows (see Chapter 10 for additional discussion). There is a growing body of work devoted to understanding the effects of volatile anesthetics and sedative agents in pediatric anesthesia which may help inform thoughtful sedation practices in the CICU. Animal models have demonstrated detrimental effects of sedative medications, such as midazolam and morphine, which can trigger neuroapoptosis [262, 263]. The jury is still out, however, regarding long-term effects of these medications in human infants and children. Although there is concern that they could have negative neurocognitive effects, some studies do not support this hypothesis. For example, a prospective study examining the neurodevelopmental outcomes in infants following exposure to sedative and analgesic drugs for complex cardiac surgery found no association between sedation/analgesia and mental, motor, or vocabulary delay [264]. Interestingly, dexmedetomidine (a CNS α2-adrenergic receptor agonist) has been found to have neuroprotective properties, and a recent retrospective study found that it may improve neurodevelopmental outcomes and protect against adverse effects of general anesthesia in infants with CHD [265]. It will be important to continue research in this field and modify CICU sedation/analgesia practices based on findings from future studies in this fragile patient population.

Longitudinal follow-up of neonates and infants who have undergone cardiac surgery demonstrates that the risk of long-term neurodevelopmental abnormalities is most likely the result of an interplay among preexisting brain injury, perioperative risk factors, and patient-specific factors (e.g., type of congenital heart lesion, socioeconomic status, gestational age, presence of genetic abnormalities). Prolonged LOS in the CICU has also been associated with worse cognitive outcomes, even when adjusting for perioperative events and sociodemographic variables [266]. Moreover, postoperative infants with CHD have impairments in autonomic, motor, attention, and state regulation [267]. CICU providers are becoming more cognizant of the disruptive and unnatural environment in an ICU and are beginning to focus on providing developmentally-appropriate and family-focused care [268]. Neurodevelopmental abnormalities appear to be most pronounced in the single ventricle population, especially those with HLHS [221, 269]. Motor deficits are significantly worse than cognitive deficits at 1 year of age. More sophisticated neuropsychological testing can be performed in older patients, and detailed follow-up of the Boston Circulatory Arrest Study group in adolescence revealed impairments in memory, visual–spatial skills, executive function, attention, and social integration [270]. A significant proportion of these patients also required academic and behavioral services, with 33% receiving tutoring and 25% receiving special education. Children with repaired congenital heart defects, in later infancy and childhood, have had more encouraging neurodevelopmental results, with one study demonstrating test results within the population normative range [271]. These long-term assessments of neurodevelopment underscore the need for the creation of integrated support systems, including physical/occupational/speech therapy, academic support, and psychological counseling to assist these at-risk children following hospital discharge. Organizations, such as the Cardiac Neurodevelopmental Outcome Collaborative, have been created to study and optimize neurodevelopmental outcomes in patients with CHD. Chapter 14 has an extensive discussion of neurological monitoring and outcomes.

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KEY POINTS: NEUROLOGIC MONITORING/ ASSESSMENT AND COMPLICATIONS

- Children who undergo surgical intervention as neonates and young infants appear to be at the greatest risk for the subsequent development of neurologic, developmental, and psychiatric disabilities.
- Neonates with CHD, particularly those with D-TGA and severe LV outflow tract obstruction, frequently demonstrate evidence of brain immaturity on MRI.
- Prolonged LOS in the CICU is associated with worse cognitive outcomes, even when adjusted for perioperative events and sociodemographic variables.
- The clinical manifestations of stroke are age dependent, with infants typically demonstrating altered mental status and seizures, while older children display focal neurologic deficits associated with specific cerebrovascular territories.

Fluid management and renal dysfunction

Fluid overload and renal dysfunction are important sources of morbidity and occasional mortality in the CICU. Data from the general pediatric critical care population reveal that increasing degrees of fluid overload are an independent predictor of pulmonary dysfunction, increased length of hospitalization, and mortality [272–275]. Subsequent evaluations in the postoperative cardiac population demonstrate similar findings, with fluid overload associated with longer exposure to inotropes and mechanical ventilation, longer hospital stays, development of AKI, and mortality [273, 276–280]. AKI in postoperative cardiac surgery patients has been shown to be associated in one study with younger age (particularly infants), higher surgical complexity, cyanotic lesions, longer CPB times and use of DHCA, and higher postoperative vasoactive-inotrope scores [281–283]. Two large, single-center reports also indicate that single ventricle physiology is an independent risk factor for AKI [284, 285]. Fluid overload and AKI in the cardiac surgical population are influenced by both intraoperative factors (e.g., ischemia–reperfusion injury and hypothermia from CPB, maladaptive inflammatory response to oxidative stress with capillary leak and interstitial fluid accumulation) and postoperative factors (e.g., endothelial dysfunction and capillary leak, LCOS, nephrotoxic medication administration, volume resuscitation, vasomotor instability) [281, 286, 287]. Early postoperative fluid overload is also compounded by volume replacement with crystalloid, colloid, and/or blood products in the CICU in response to progressive hemodynamic compromise from intravascular depletion secondary to capillary leak. The youngest patients, particularly neonates and young infants, who tend to have longer CPB support times, are the population at greatest risk for the development of capillary leak syndrome [288]. Subsequent development of an LCOS and increased secretion of antidiuretic hormone also contribute to fluid overload and AKI by means of renal dysfunction and delayed water clearance, which may progress to renal failure if LCOS persists. Most patients develop mild degrees of AKI by postoperative day 1 and recover within 2–3 days. Patients with increasing severity of AKI are more likely to have prolonged ventilation days and longer ICU/hospital stays [282–284]. In addition, children undergoing multiple cardiac surgeries have higher odds of developing AKI with subsequent surgeries, especially if AKI developed with earlier surgeries [289]. Long-term evaluations of children who developed postoperative AKI demonstrate an increased incidence of chronic kidney disease and hypertension at 5-year follow-up [290].

Management of fluid overload begins in the OR through the initiation of ultrafiltration. Ultrafiltration is a technique that removes low-molecular-weight solutes and plasma water through convection using hydrostatic forces to filter these substances across a semipermeable membrane. The use of conventional ultrafiltration during CPB as well as modified ultrafiltration after CPB cessation has been shown to reduce fluid accumulation in the early postoperative period, improve early postoperative hemodynamics including measured CI, decrease postoperative blood loss and blood product use, improve lung compliance with decreased duration of mechanical ventilation, improve ventricular function, and decrease ICU LOS [291–297]. Intraoperative glucocorticoids have also been used for many years to blunt the inflammatory effects of CPB; although decreased laboratory evidence of inflammation is achieved, this intervention has not been proven to result in significant improvement in clinical outcomes [298].

Fluid management post-CPB in the CICU commences with restriction of maintenance IV fluids to 50–75% of full maintenance and is coupled with judicious use of fluid replacement and vasoactive/inotropic support titrated to appropriate filling pressures and hemodynamic response. Once the patient has achieved greater hemodynamic stability and any capillary leak process has subsided, IV diuretics are instituted to accelerate fluid removal and assist with the reduction in mechanical ventilator support. Furosemide (1 mg/kg IV every 6–8 hours) is a commonly-prescribed loop diuretic that must be excreted into the renal tubular system before producing diuresis. Low CO, therefore, reduces its efficacy. Bolus dosing may result in a significant diuresis over a short period, leading to intravascular depletion and the potential for hypotension. A continuous furosemide infusion (0.1–0.3 mg/kg/hour) after an initial loading dose as a bolus may provide a more consistent and sustained diuresis without inducing sudden fluid shifts and hemodynamic lability. Chlorothiazide (5–10 mg/kg IV or PO every 6–12 hours) is also an effective diuretic, particularly when used in conjunction with loop diuretics (with chlorothiazide preceding furosemide administration by ~30 minutes when administered as intermittent dosing). Low-dose dopamine (3–5 mcg/kg/min), in addition to supporting CO, may increase renal blood flow and promote diuresis. Fenoldopam (0.1–0.5 mcg/kg/min), a selective dopamine-1 receptor agonist, may also assist in optimizing diuresis by reducing renal vascular resistance and enhancing renal perfusion; however, results of its effects on urine output and fluid balance status in young children after CPB are mixed [299, 300]. Nesiritide (0.005–0.03 mcg/kg/min), a recombinant form of brain natriuretic peptide (BNP) identical to endogenous BNP, has

been approved to treat adult acute decompensated heart failure. It can be added to the diuretic regimen as an adjunct to encourage diuresis. Its cardiac effects include increased lusitropy through a reduction in cytosolic calcium, leading to cardiac myocyte relaxation. In the kidney, it promotes diuresis through afferent arteriolar vasodilation and efferent arteriolar vasoconstriction. The limited reports of its use in the pediatric population suggest that it can be used safely in the pediatric heart failure population to promote diuresis [301–303]. However, caution is advised with the use of nesiritide, as administration has been associated with worsening renal function and risk for mortality in adults with decompensated heart failure. This has led to a rapid decline in its use overall and associated reduction in its use in pediatrics in the setting of insufficient data [304, 305].

AKI occurs commonly in the CICU, with a reported incidence of 15–60% [281–285, 306]. This wide range of reported incidence is likely due to use of differing criteria to define AKI, as well as examination of different study populations. The most commonly used criteria to define AKI are the pediatric RIFLE (pRIFLE), AKIN, and KDIGO criteria (Table 36.10). The pRIFLE criteria were developed as a pediatric application of the adult RIFLE criteria, an acronym standing for risk, injury, failure, loss, and end-stage kidney disease [307, 308]. Patients are grouped into three categories (corresponding to AKI) based on progressive declines in urine output and estimated Cr clearance via the Schwartz equation. The AKIN criteria define three stages based on progressive increases in serum Cr from baseline, with a minimum increase of 0.3 mg/dL, and it categorizes any patient receiving renal replacement therapy (RRT) as failure [309]. The KDIGO criteria, which was created in 2012 by harmonizing the adult RIFLE, pRIFLE, and AKIN criteria with validation in both pediatrics and adults, rely on rise in serum Cr and changes in urine output. It is defined in three stages based on the degree of serum Cr rise above baseline and extent of urine output [310].

While serum Cr has traditionally been used as the gold standard for the assessment of renal function, assessments of AKI based on increases in serum Cr may delay diagnosis and render interventions ineffective, as renal injury occurs well before changes in Cr levels are reflected in serum measurements. Extensive basic and translational science research has yielded the discovery of several emerging biomarkers that may allow for a more rapid diagnosis of AKI. The best-described biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), IL-8, liver fatty acid-binding protein (L-FABP), and kidney injury molecule-1 (KIM-1). All of these biomarkers have been studied in the post-CPB population, and single-center studies have been shown each to be independent predictors of AKI [311–316]. When these same biomarkers were evaluated in prospective, multicenter observational studies, they did not perform as well, particularly in discriminating mild AKI, but they were predictive of more severe degrees of AKI [317, 318]. Further research is ongoing regarding the use of biomarkers in the diagnosis of AKI and their potential for the evaluation of therapeutic interventions.

There are currently no recognized medical therapies for the treatment of AKI in the pediatric population. *N*-acetylcysteine (NAC) has known antioxidant properties and has been used historically to prevent or attenuate renal injury related to IV contrast exposure for radiologic studies. Multiple randomized, placebo-controlled studies in adults have failed to demonstrate any clear benefit of NAC in the prevention of AKI, and its use for this purpose in the pediatric population has not been reported [319]. Aminophylline in a single-center retrospective study has been reported to improve renal excretory function and augment urine output in CICU patients with oliguric AKI [320]. A comparative retrospective study between diuretic and aminophylline intraoperatively for oliguria showed similar urine output at 48 hours after surgery with no difference in AKI; less RRT use occurred in the aminophylline group [321]. A randomized, double-blinded, placebo-controlled study examining aminophylline use in the postoperative pediatric cardiac population found no difference in rate or severity of AKI, fluid balance, or urine output [322].

When AKI progresses to renal failure, RRT may be indicated to treat fluid overload, severe electrolyte or metabolic derangements, and symptomatic uremia and to address fluid restriction, which limits the delivery of adequate nutritional support. A peritoneal dialysis (PD) catheter may be placed intraoperatively or postoperatively for either simple drainage with the goal of reducing intra-abdominal pressure or the institution of true PD. Reports on prophylactic placement of PD catheters with early institution of dialysis in the immediate postoperative period to relieve fluid overload have shown shorter time to achievement of negative fluid balance, decreased duration of mechanical ventilation, and decreased inotrope scores [323]. A randomized clinical trial of PD versus furosemide for the prevention of fluid overload in postoperative cardiac patients showed the PD group to have a lesser degree of fluid overload, shorter inotrope use duration, and fewer electrolyte imbalances, but there were no differences in mortality [324]. Earlier PD initiation has been shown to be associated with better clinical outcomes and survival advantage in one study [325]. Complications of PD catheter placement and use include infection and injury to abdominal organs, but PD use is generally safe with minimal rate of adverse events [324, 326, 327]. It is important to note that a persistent communication between the peritoneum, mediastinum, and/or pleural cavities early following surgery may limit the effectiveness of PD. A more recent meta-analysis suggests that PD use may be associated with increased odds of mortality, indicating that further evaluation of the efficacy of PD use in postoperative pediatric cardiac surgical patients is indicated [328].

Double-lumen, large-bore catheters may also be inserted into a large systemic vein to institute intermittent hemodialysis or CRRT. As postoperative cardiac patients frequently will not tolerate the larger fluid shifts generated through intermittent hemodialysis, CRRT is typically the modality of choice and is more efficient than PD in both fluid and solute removal. Complications related to this therapy include infection, catheter-related venous thrombosis, and potential hemodynamic instability related to fluid shifts. In the general pediatric intensive care population, an association between mortality and increasing degrees of fluid overload prior to CRRT initiation is reported, suggesting that earlier initiation of this therapy may be beneficial [329]. For pediatric cardiac patients, data suggests that the risk of requiring CRRT is higher in children undergoing cardiac surgery, and that the need for CRRT after cardiac surgery is associated with higher

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Table 36.10 Criteria to define acute kidney injury in pediatrics

pRIFLE			Adult RIFLE			AKIN		KDIGO		
Class	**Urine output**	**eCrCl by Schwartz**	**Class**	**Urine output**	**sCr or GFR**	**Stage**	**sCr**	**Stage**	**sCr**	**Urine output**
Risk	<0.5mL/kg/hr × 8 hours	eCrCl ↓ by 25%	Risk	<0.5mL/kg/hr × 8 hours	↑sCr by 150% or GFR ↓ by 25%	I	↑sCr>0.3mg/dL or ↑sCr>150–200% from baseline	I	1.5–1.9 × baseline or ≥0.3mg/dL (≥26.4μmol/l) increase	<0.5mL/kg/hr for 6–12hours
Injury	<0.5mL/kg/hr × 16 hours	eCrCl ↓ by 50%	Injury	<0.5mL/kg/hr × 16 hours	↑sCr by 200% or GFR ↓ by 50%	II	↑sCr to >200–300% from baseline	II	1.0–2.9× baseline	<0.5mL/kg/hr for ≥12hours
Fail	<0.3mL/kg/hr × 24 hours or Anuric ×12 hours	eCrCl ↓ by 75% or <35mL/min/1.73m^2	Fail	<0.3mL/kg/hr × 24 hours or Anuric ×12 hours	↑sCr by 300% or >4mg/dL with an acute ↑ of 0.5mg/dL or GFR ↓ by >75%	III	↑sCr of >300% from baseline or sCr>4mg/dL with an acute ↑ of at least 0.5mg/dL	III	3.0 × baseline or sCr≥4.0mg/dL (≥353.6μmol/l) or initiation of RRT or eGFR<35mL/min/1.73m^2 (<18 years)	<0.3mL/kg/hr for ≥24hours or Anuric for ≥12hours
Loss ESRD	Failure >4 weeks Failure >3 months		Loss ESRD	Failure >4 weeks Failure >3 months						

RIFLE – Risk, Injury, Failure, Loss, End-Stage; pRFILE – pediatric RIFLE; AKIN – Acute Kidney Injury Network; eCrCl – estimated creatinine clearance; RRT, renal replacement therapy, sCr – serum creatinine; GFR-glomerular filtration rate; e GFR - estimated GFR; ESRD – end-stage renal disease; ↑ - increase; ↓ - decrease
Source: Cooper et al [288] and Khwaja et al [310]

mortality. Similar to the experience of PD, earlier initiation of CRRT may lead to lower mortality when compared to later use [330, 331]. In addition, with the development of CRRT devices that can be used in neonates and infants as small as 2.5 kg (central venous catheter sizes ranging from 4 to 7 Fr), the application of CRRT to younger and smaller patients may be on the horizon [332, 333].

Aquapheresis is another modality for patients needing only fluid removal and not solute clearance. It has been used in adult heart failure patients and can be deployed in children with smaller catheters and a smaller module with lower extracorporeal volumes; this reduces blood product exposure because a blood prime is no longer required [334]. Thus far, data on aquapheresis use in pediatrics and pediatric cardiac patients are limited, thus warranting further evaluation [335–337]. A prospective registry study looking at the utility and safety profile of aquapheresis in pediatric populations is currently underway.

KEY POINTS: FLUID MANAGEMENT AND RENAL DYSFUNCTION

- Neonates and young infants who have been exposed to longer CPB times are the population at greatest risk for the development of capillary leak syndrome and AKI.
- Patients with AKI after cardiac surgery are more likely to require prolonged support with mechanical ventilation, longer hospitalizations, and increased inotropic support, and their risk of mortality is increased.
- Several emerging biomarkers that may allow for a more rapid diagnosis of AKI, including NGAL, cystatin C, IL-18, L-FABP, and KIM-1, have recently been described.
- Fluid restriction and diuretic therapy continue to be the primary treatments to reduce postoperative fluid overload in the CICU.
- PD and hemodialysis should be considered in patients with fluid overload refractory to diuretic therapy, severe electrolyte or metabolic derangements, symptomatic uremia, and inadequate nutrition.
- Although the need for CRRT in the postoperative period for pediatric cardiac surgery patients is associated with overall worse outcomes, early initiation of CRRT appears to mitigate this effect to some extent, and newer devices allow CRRT to be applied safely in children weighing 5 kg or less.

Nutrition and gastrointestinal complications

Adequate delivery of nutrition is a vital component in the care of critically ill children. Several studies in the pediatric and adult critical care population have underscored the importance of nutritional therapy by demonstrating its role in reducing the incidence of infection, duration of mechanical ventilation, and length of hospital stay [338–340]. Despite the importance of optimizing nutritional intake, there are often multiple barriers to the delivery of adequate calories to patients in the CICU. These barriers include dynamic changes in energy expenditure, particularly in the early postoperative period, and the need for postoperative fluid restriction. Parenteral nutrition (PN) is frequently employed in the early postoperative period secondary to concerns regarding systemic or splanchnic hypoperfusion and feeding intolerance. However, a recent multicenter trial has shown that withholding PN for up to 1 week has been clinically superior with respect to infection rate and length of mechanical ventilation when compared with the strategy of providing early PN [341].

These data have put into question the current paradigm of early PN in postoperative pediatric cardiac patients, as this study showed greater risk for nosocomial infection in the early PN group. The duration of mechanical ventilatory support was shorter, and the likelihood of being weaned alive earlier from mechanical ventilation was higher among patients receiving late PN than among those receiving early PN. This may be due to the fact that earlier PN makes fluid management more challenging and overestimates caloric needs. In fact, a recent systematic review demonstrated that indirect calorimetry-guided energy delivery prevented the well-known risks of under- and overfeeding and reduced short-term mortality in critically ill patients [342]. It is likely that a subset of early postoperative patients may have reduced total energy expenditure, similar to hibernation, and thus standard calculations of total energy expenditure may overestimate energy requirements and thus impose an unnecessary ventilatory load.

As in the critically ill adult population, stress ulceration and gastritis can occur in pediatric patients; historically, universal stress ulcer prophylaxis (SUP) has been recommended. Recently, however, this paradigm has been reassessed, and the risk of harm from SUP has been demonstrated in pediatric and adult ICU patients. The SUP ICU trial was a multicenter trial that demonstrated no mortality benefit between IV pantoprazole and placebo, despite a reduction in clinically significant gastrointestinal (GI) bleeding [343]. In pediatric patients, the data are observational, but they demonstrate that clinically significant bleeding is rare, multiagent prophylaxis common, and complications are frequently associated [344]. In addition, a number of meta-analyses have demonstrated risks with SUP for ventilator-associated pneumonia in enterally fed adult [345] and PICU patients [346].

Postanesthesia nausea and vomiting are frequent in the early postoperative period, particularly in patients who have been fast-tracked to extubate either in the OR or within several hours of arriving in the CICU. The use of antiemetics, such as 5-HT_3-receptor antagonists, H_1-histamine receptor antagonists, benzodiazepines, anticholinergics, and dexamethasone, may be helpful in mitigating this response.

Early resumption of enteral nutrition is encouraged to reduce the risk of nosocomial pulmonary and bloodstream infections by preventing bacterial overgrowth and to minimize complications associated with the delivery of parental nutrition, including catheter-related infection and liver injury or cholestasis. The use of feeding algorithms (one example is shown in Figure 36.9) has been demonstrated to improve the introduction of enteral nutrition following cardiac surgery [347, 348], although no one specific algorithm has been demonstrated to be superior. Unfortunately, the introduction of enteral nutrition can be compromised by the presence of splanchnic hypoperfusion due to LCOS or from low diastolic pressure in patients with runoff from systemic-to-PA shunts or a large PDA in the preoperative period. Clinical

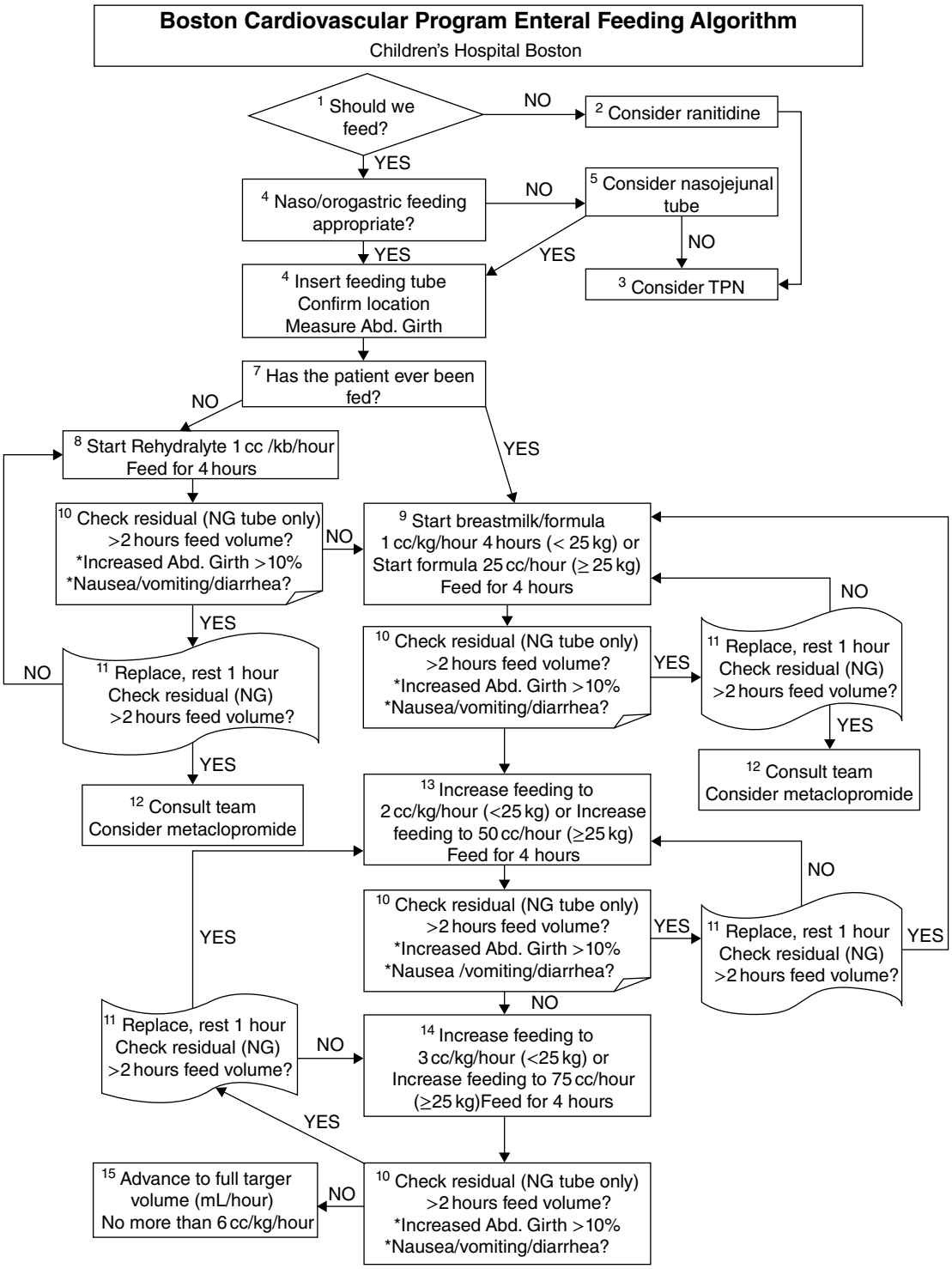


Figure 36.9 Feeding algorithm. (Source: Braudis et al. [347]. Reproduced with permission of Wolters Kluwer Health, Inc.)

manifestations of splanchnic hypoperfusion range from feeding intolerance and ileus to necrotizing enterocolitis [349]. The onset of abdominal distension, bloody stool, and pneumatosis intestinalis on abdominal radiograph suggests necrotizing enterocolitis. Severe cases may also demonstrate signs of abdominal wall cellulitis, sepsis, hemodynamic instability, and gut perforation. Initial treatment includes discontinuation of enteral feeds, support with PN, and broad-spectrum IV antibiotics [350]. Hemodynamic support may be necessary, and occasionally laparotomy if perforation occurs or hemodynamic instability persists.

Other causes of feeding intolerance in the pediatric cardiac population include bowel edema following CPB, delayed gastric emptying secondary to opioid use for perioperative analgesia, gastroesophageal reflux, vocal cord dysfunction, and small bowel obstruction secondary to malrotation,

particularly in the heterotaxy population [351, 352]. Patients with decreased ventricular function may be unable to increase their CO sufficiently to meet the metabolic demand associated with oral feeding and the absorption of food. Coexisting respiratory problems such as tachypnea may also restrict oral intake. Placement of an enteral feeding tube is helpful to ensure adequate nutritional intake in these circumstances. Transition from nasogastric to transpyloric feeding may also be considered in patients with delayed gastric emptying, respiratory compromise requiring noninvasive PPV with accompanying gastric insufflation, and severe gastroesophageal reflux. In addition, progressive increases in the caloric density of enteral feeds (e.g., from 20 to 28–30 calories/oz) are frequently required to meet patient metabolic demands and prevent fluid overload. Consultation with a registered dietician, assessment of somatic growth by measuring serial weights, analysis of nutritional status via biochemical markers (i.e., albumin, prealbumin, and transferrin), and consideration of indirect calorimetry to assess resting energy expenditure can assist in ensuring the adequate delivery of calories [353].

Liver dysfunction may also occur in CICU patients. It is typically related to a persistent LCOS causing ischemic hepatitis or complications related to CPB, including inadequate venous drainage from the lower body and low perfusion pressure. Patients following a Fontan procedure may be at particular risk because of hepatic venous congestion from persistently elevated central venous pressure. Marked elevations in liver transaminases may be detected within hours of surgery and remain elevated for 2–3 days before gradually returning to normal. These patients typically have elevated prothrombin time and PPT as well and are thus at increased risk of bleeding complications. However, fulminant hepatic failure is uncommon.

Finally, the presence of chylothorax can pose a significant challenge to establishing adequate nutrition and enteral feeding. Chylous effusions tend to be milky in appearance, have a cell count of predominantly lymphocytes (>80%), and test positive for triglycerides. Standardized diagnostic criteria and subsequent management strategies are lacking, further exacerbating compromised nutritional status in these complex patients. Generally, initial steps involve transitioning to a medium-chain triglyceride or low-fat diet. For persistent, high-output losses (>10 mL/kg/day), cessation of feeds, and initiating total PN are subsequent steps; NPO periods may last anywhere from 5 to 21 days. Additional treatment interventions vary among institutions and availability of expertise and resources [354].

KEY POINTS: NUTRITION AND GASTROINTESTINAL COMPLICATIONS

- Patients in the CICU are often malnourished from the catabolic state induced by CHF and postoperative stress, as well as fluid restriction secondary to capillary leak and renal dysfunction.
- Enteral nutrition may be compromised by splanchnic hypoperfusion due to low CO or from low diastolic pressure in patients with runoff systemic-to-PA shunts.
- The use of feeding algorithms has been demonstrated to improve the introduction of enteral nutrition following cardiac surgery.
- Postoperative chylothorax further compromises nutritional challenges.

SARS-CoV-2 infection and multisystem inflammatory syndrome in children

Since its emergence late in 2019, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global pandemic resulting in the loss of millions of lives, significant and persistent health complications in those who survive severe infection, and disruption of the global economy and geopolitical climate [355–358]. In April 2020, reports began to emerge of a new clinical entity affecting children associated with SARS-CoV-2 in different regions of the world. The clinical presentation was similar to the hyperinflammatory responses described in Kawasaki disease (KD), toxic shock syndrome (TSS), and hemophagocytic lymphohistiocytosis/macrophage activating syndrome (HLH/MAS) and occurred following prior exposure to/infection with SARS-CoV-2 [357, 359–361]. The term "Multisystem Inflammatory Syndrome in Children" (MIS-C) has since been given to this newly documented and distinct condition.

The case definition for MIS-C includes the following: (i) age <21 years, (ii) fever ≥38 °C for ≥24 hours *or* subjective fever lasting ≥24 hours, (iii) lab evidence of inflammation (e.g., abnormal C-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-dimer, ferritin, lactate dehydrogenase, procalcitonin, IL-6), (iv) severe illness requiring hospitalization with ≥ two organ system involvement (e.g., cardiac, renal, respiratory, hematologic, GI, dermatologic, neurologic), (v) no alternate plausible diagnosis, and (vi) current or recent SARS-CoV-2 infection by polymerase chain reaction (PCR)/serology/antigen test *or* exposure to suspected/confirmed COVID-19 case within the previous 4 weeks prior to onset of symptoms [362–364]. MIS-C is thought to be a post-viral inflammatory response resulting in organ dysfunction (e.g., decreased myocardial performance) and not secondary to unremitting infection [363]. Although the majority of children infected with SARS-CoV-2 experience mild-to-minimal disease, severe disease in children has been noted [363–365]. As more cases of both severe infection in children with SARS-CoV-2 requiring hospitalization and MIS-C arise, additional data support that differences do exist between these two entities [365]. In MIS-C, serologic antibody testing is frequently positive while PCR may be negative, the median age is older for MIS-C than in children hospitalized with severe COVID-19 infection, there is an increased incidence of MIS-C in children of African/Afro-Caribbean descent, and those with MIS-C are more likely to have cardiorespiratory or isolated cardiovascular involvement with myocardial dysfunction and shock as presenting symptoms [365]. The degree of cardiovascular involvement, older age at presentation, and elevated cardiac enzymes and BNP along with a higher degree of inflammatory markers can also help distinguish MIS-C from KD. Cardiovascular involvement in MIS-C includes LV systolic dysfunction of varying degrees, arrhythmias, pulmonary edema secondary to elevated left heart filling pressures from diastolic dysfunction, coronary artery aneurysms (CAAs), elevated serum troponin and BNP levels, and cardiovascular collapse requiring CPR and ECMO [365, 366]. GI symptoms are also common in those with MIS-C. In children with either potential or diagnosed MIS-C, early consideration of admission to an ICU (preferably a CICU with experience in

managing myocarditis and cardiogenic shock) should be considered.

Although a significant amount of literature exists on respiratory management strategies in adults with severe SARS-CoV-2 infection requiring mechanical ventilation, data and consensus guidelines on respiratory management in children with severe SARS-CoV-2 infection are currently lacking. This is due, in large part, to minimal-to-mild illness in most pediatric patients infected with SARS-CoV-2. Initial large-scale adult clinical data utilized a higher degree of PEEP use for hypoxemia and increased utility of prone positioning along with successful use of noninvasive ventilatory support [367]. Over time and with more experience using different ventilation strategies in patients with SARS-CoV-2 and severe respiratory involvement, treatment approaches have changed to promote noninvasive ventilatory support and less emphasis on institution of early invasive mechanical ventilation. In addition, high empiric PEEP strategies for hypoxemia in otherwise fairly compliant lungs are no longer considered favorable due to significant hemodynamic impairment secondary to high PAP [368]. In children with severe respiratory involvement with SARS-CoV-2, the pediatric acute respiratory distress consensus guidelines appear to be beneficial. These include early consideration of noninvasive PPV, permissive hypercapnia, tidal volumes 5–8 mL/kg, moderately elevated PEEP, inspiratory plateau pressure <32 cmH_2O, alveolar recruitment maneuvers, SpO_2 levels >88%, goal-directed fluid management, and minimizing systemic metabolic demand while optimizing systemic oxygen delivery [369].

MIS-C with cardiovascular or cardiorespiratory involvement should be treated similarly to children presenting with myocarditis. Achieving appropriate gas exchange while maintaining lung volumes at FRC may require NIV or invasive ventilation strategies. Although children commonly present as comfortably tachypneic, intubation and invasive mechanical ventilation may be indicated for progressive hypoxemia, altered mental status, or failure to improve respiratory distress despite initiation/escalation of noninvasive PPV. The use of personal protective equipment (PPE) during the aerosol-generating process of intubating a patient with known SARS-CoV-2 infection or patient under investigation (PUI) for SARS-CoV-2 infection is of paramount importance. This includes at a minimum a properly fitted N95 mask and sufficient eye protection, as well as gown and double gloves. Under some conditions, this may result in the need for higher levels of protection, such as a powered air-purifying respirator. This process requires adherence to specific institutional polices regarding essential staffing so that provider exposure inside and outside the patient room is minimized, appropriate donning/doffing techniques for PPE are used, and a closed ventilator circuit with ventilator filters is maintained [370]. Procedures in which the ventilator system must be opened to the environment should be minimized as much as possible, as this increases the risk of aerosolizing potentially infectious viral particles.

In children presenting with MIS-C and LV systolic dysfunction complicated by pulmonary congestion due to heart failure, PPV may both re-recruit collapsed alveoli and improve respiratory distress. Furthermore, PPV in this setting will also decrease LV afterload, increase LV stroke volume, and lower myocardial oxygen demand. Myocardial dysfunction culminating in cardiogenic shock occurs commonly in MIS-C [366], and the initiation of inotropic and/or inodilator support (e.g., epinephrine, dopamine, dobutamine, and milrinone) is recommended to improve CO and systemic oxygen delivery. If a child is presenting instead in distributive shock secondary to the immune-dysregulated response associated with MIS-C, peripheral vasoconstricting agents can be administered (e.g., norepinephrine, vasopressin). If IV volume expansion is indicated to support an adequate blood pressure, providing gentle resuscitation with small volume boluses in 5 mL/kg aliquots with frequent reevaluation of the CO examination and respiratory examination is suggested to reduce the likelihood of creating fluid overload in the setting of systolic and/or diastolic heart failure.

After an initial evaluation measuring serum troponin and BNP levels, trending these values through the hospitalization should be considered. An ECG and echocardiogram should be performed early in cases of diagnosed or suspected MIS-C to document the cardiac rhythm and conduction and assess the degree of myocardial injury/ischemia, myocardial dysfunction, and the appearance of the coronary arteries (both their dimensions and to look for aneurysms). Continuous ECG monitoring and telemetry are warranted due to the incidence of arrhythmias in children with MIS-C [365, 366]. Similar to classic myocarditis, the presence of arrhythmias in MIS-C should be closely monitored and treated in consultation with cardiac electrophysiology consultants; arrhythmias may serve as a marker for significant myocardial dysfunction/irritability, which can lead to clinical decompensation. The severity of LV systolic dysfunction can vary in MIS-C [365, 366], while RV systolic dysfunction appears to be quite rare [366]. However, studies to date report that the vast majority of patients have a normalization of LV systolic function over time [365, 366]. As MIS-C and KD share a vasculitis component caused by a postviral inflammatory response as a possible etiology, CAAs have been described in MIS-C, and they warrant treatment with high-dose intravenous immune globulin (IVIG) along with high-dose aspirin. Close monitoring during and after the hospitalization to evaluate for regression of CAAs should be performed similar to treatment guidelines for KD [371].

As our understanding of MIS-C develops further, treatment options are likely to evolve over time. At the time this chapter was updated, high-dose IVIG (2 g/kg), methylprednisolone, and low-dose aspirin remain the most commonly accepted therapeutic treatments [357, 362–364, 366] for MIS-C, with IVIG and glucocorticoids being used either alone or in combination. One study suggests that recovery from MIS-C did not differ after primary treatment with IVIG alone, glucocorticoids alone, or IVIG+glucocorticoids; however, differences in outcomes may emerge as additional data accrues [372]. Additional therapies that can be considered in consultation with appropriate subspecialty services include IL-2 receptor antagonists and IL-6 receptor antagonists. The presence of a variety of potential treatments emphasizes that we do not yet have a specific treatment regimen that is clearly documented to be effective in changing the course of MIS-C. Careful consideration should be given to the use of high-dose IVIG, as this constitutes a large IV volume load that may not be well tolerated in the setting of myocardial dysfunction. Mitigation tactics for this risk include administration of IVIG slowly or using lower volume aliquots along with the addition of diuretic therapy. As the inflammatory response in MIS-C can result in

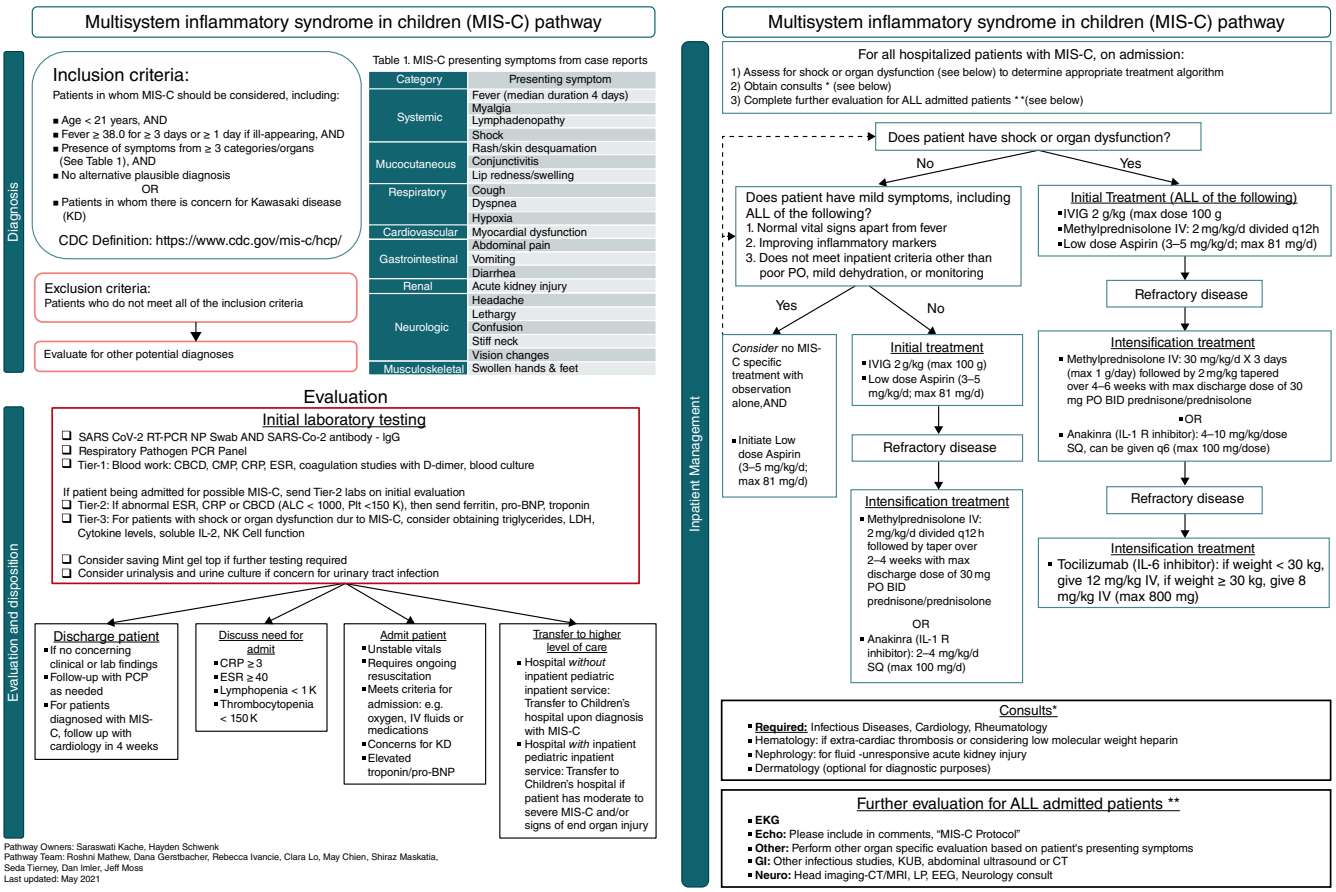


Figure 36.10 Lucile Packard Children's Hospital Stanford MIS-C clinical pathway. (Source: Reproduced with permission from S. Kache et al.).

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a prothrombotic state, anticoagulation with heparin or enoxaparin and antiplatelet agents is strongly recommended [357].

A multidisciplinary approach to management of the child presenting with MIS-C is of paramount importance, and the involvement of cardiology, infectious diseases, and rheumatology services is recommended. The role of the cardiac intensivist in coordinating the evaluations and considerations of these and other subspecialty services (e.g., hematology, nephrology, gastroenterology, neurology, dermatology) in MIS-C cases will optimize the support and treatment strategies offered to the child admitted to the CICU. The use of ECMO in children with MIS-C with refractory cardiogenic shock or those who experience IHCA is supported by the limited published literature, and the outcomes in MIS-C patients supported with ECMO have been reassuring to date [365, 366]. Currently, no guidelines exist that clearly support the use of cardiac catheterization to obtain endomyocardial biopsies in the prognostication or risk stratification of MIS-C; however, follow-up cardiac MRI may be useful for that purpose [357]. Cardiac catheterization to assess hemodynamics and consider interventions (e.g., BAS while supported on peripheral VA-ECMO) may be considered by the cardiac intensivist if the general course of myocarditis is not following an improving trajectory.

Institutional practices in the evaluation and management of children with MIS-C may vary, and the reader is advised to refer to the MIS-C guidelines in use at their respective institution/practice. One example of an institution-specific MIS-C pathway can be found in Figure 36.10. This pathway, which was developed at Lucile Packard Children's Hospital Stanford and last updated in May 2021, highlights inclusion criteria, laboratory testing, indications for admission, indications for treatment, treatment options, diagnostic and consultation considerations, anticoagulation therapy, and respiratory/cardiogenic shock management considerations. As we continue to learn more about the impact of SARS-CoV-2 active infection and the postinfectious inflammatory response that constitutes MIS-C and its place along a continuum with KD/TSS/HLH/MAS, therapies and optimal practice patterns will continue to be revised and improved. The reader of this section is strongly advised to evaluate the most up-to-date literature regarding SARS-CoV-2 infection in children and MIS-C when caring for patients with these newer disease processes.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 McGoon DC, Mair DD. On the unmuddling of shunting, mixing, and streaming. J Thorac Cardiovasc Surg 1990;100:77–82.
An expert review of shunting, mixing, and streaming as it pertains to cardiac physiology and the hemodynamic characteristics that differentiates one term from the other. This overview assists in clarifying for the reader the differences between each term by using hemodynamic examples and specific cardiac anatomic lesions.

20 Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. Arch Dis Child 1999;80(5):475–80.
Review of the key aspects of cardiopulmonary interactions as it pertains to forms of congenital heart disease. Details the effects of positive pressure ventilation on preload and afterload of the right and left ventricle.

30 Mahle WT, Nicolson SC, Hollenbeck-Pringle D, et al. Utilizing a collaborative learning model to promote early extubation following infant heart surgery. Pediatr Crit Care Med 2016;17(10):939–47.
Multicenter study evaluating the use of learning sessions, development of a clinical practice guideline, and expert site visits to promote early extubation for index cardiac surgeries (VSD and TOF repair). A collabortive learning strategy did significantly increase the rate of early extubation, but did not significantly change the postoperative ICU length of stay.

42 Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107(7):996–1002.
A multicenter, randomized, double-blind, placebo-controlled trial evaluating the use of prophylactic milrinone in preventing low cardiac out syndrome in pediatric patients after cardiac surgery. High-dose milrinone significantly reduced the risk of low cardiac output syndrome after pediatric congenital heart surgery.

82 Gaies M, Pasquali SK, Banerjee M, et al. Improvement in pediatric cardiac surgical outcomes through interhospital collaboration. J Am Coll Cardiol 2019;74(22):2786–95.
Membership in a quality improvement collaborative with transparent data sharing and collabortive learning demonstrates improved outcomes for patients undergoing complex pediatric cardiac surgery.

103 Marino BS, Tabbutt S, MacLaren G, et al.; American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Emergency Cardiovascular Care Committee. Cardiopulmonary resuscitation in infants and children with cardiac disease: a scientific statement from the American Heart Association. Circulation 2018;137(22):e691-e782.
Expert review and scientific statement with practice guideline recommendations from the American Heart Association for cardiopulmonary resuscitation (CPR) in children with heart disease. This statement details recommendations for resuscitation by levels of evidence for varying cardiac disease processes and provides a thorough review of resuscitation management and post-arrest care.

105 Lasa JJ, Rogers RS, Localio R, et al. Extracorporeal cardiopulmonary resuscitation (E-CPR) during pediatric in-hospital cardiopulmonary arrest is associated with improved survival to discharge: a report from the American Heart Association's get with the guidelines-resuscitation (GWTG-R) registry. Circulation 2016;133(2):165–76.
A multi-center retrospective evaluation of pediatric extracorporeal cardiopulmonary resuscitation (E-CPR) deployment versus conventional-CPR for prolonged CPR duration events (≥10 minutes) during in-hospital cardiac arrest. E-CPR deployment was associated with improved survival to discharge and more favorable neurologic outcomes in survivors when compared to conventional-CPR for events where expedient return of spontaneous circulation could not be achieved.

196 Almond CS, Morales DL, Blackstone EH, et al. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation 2013;127(16):1702–11.
An analysis of the "real world experience" with the Berlin EXCOR device utilizing the combined data from the original IDE trial and the compassionate use cohort. Overall survival was 75% to transplant or recovery. Smaller patient size, end organ dysfunction pre-implant, and biventricular support were all associated with increased risk of death while on VAD support.

266 Newburger JW, Wypij D, Bellinger DC, et al. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. J Pediatr 2003;143(1):67–73.
Prolonged length of stay in the cardiac ICU was associated with worse cognitive outcomes, even when adjusted for perioperative events and sociodemographic variables.

354 Justice L, Buckley JR, Floh A, et al. Nutrition considerations in the pediatric cardiac intensive care unit patient. World J Pediatr Congenit Heart Surg 2018;9(3):333–43.
Expert review highlighting concerns and considerations for providing nutrition to pediatric cardiac intensive care patients.

CHAPTER 37
Mechanical Circulatory Support

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Background, introduction, and history

The successful use of extracorporeal membrane oxygenation (ECMO) in children began in the late 1970s when Bartlett et al. applied this technology to term newborn infants with respiratory failure [1]. In 1973, Soeter et al. described the ECMO use for cardiorespiratory failure after tetralogy of Fallot repair [2]. Later in 1987, Kanter et al. reported the first series of 13 patients with postoperative cardiac failure treated with ECMO [3]. The utilization of ECMO for cardiac support has increased steadily since the 1980s. Improved perfusion and anticoagulation techniques make the support safer so that it may be initiated earlier and not as a last resort. Data from the Extracorporeal Life Support Organization (ELSO) reveal an increase in ECMO support of 24% from 2009 to 2015, with overall survival of 62% [4]. Neonatal cardiac, neonatal, and pediatric extracorporeal life support (ECLS) to support cardiopulmonary resuscitation (CPR) have lower survival rates.

The first successful use of a left ventricular assist device (LVAD) as a bridge to heart transplant in an adult was reported by Cooley et al. in 1969 [5]. The first description of ventricular assist device (VAD) use in children was 20 years later, and the authors concluded that, as adults, VAD bridge to transplantation in children is possible [6]. In the 1990s, LVAD use in children was sporadic. However, VAD implantation in children has grown exponentially [7, 8].

Indications for mechanical support

Mechanical support can be considered for children with potentially reversible cardiac failure, respiratory failure, pulmonary hypertension (PHTN), and cardiorespiratory arrest. When used for cardiac failure, the primary goal is to rest the myocardium to allow recovery of function (bridge to recovery, BTR). Sometimes is difficult to estimate myocardial recovery, especially amid organ failure. In this situation, mechanical support can stabilize the patient before making a

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long-term decision (bridge to decision, BTD). In the absence of recovery of the myocardium, the patient may be transitioned to long-term mechanical support while awaiting a heart transplant (bridge to transplant, BTT) [9]. Adult patients can have a permanent mechanical device to support the circulation for the remainder of their lives (destination therapy, DT) if they are not heart transplant candidates (e.g. 70 years, malignancy, or severe comorbidities) [10]. Recently, several reports of DT in the pediatric population have been published [11]. The goal is not only to improve survival but also to improve the quality of life [12]. As with adults, pediatric patients, non-transplant candidates, such as those with muscular dystrophy, malignancy, comorbidities (e.g., severe obesity), or high allosensitization could be offered VAD as DT.

The indications for mechanical circulatory support (MCS) in children are often divided into two groups: those related and those unrelated to cardiac surgery (Box 37.1).

As a general principle, ECMO could potentially be used for all the indications in Box 37.1, and VAD is only considered in the absence of PHTN or respiratory dysfunction. There are pros and cons of VAD and ECMO devices, and sometimes, they are used in sequence. However, either device can be used as BTR, BTD, or BTT. The choice depends on the acuity of illness, comorbidities, the recovery potential, and anticipated duration of support [13]. In addition, if there is a choice between ECMO and VAD, a LVAD is preferable if patients are suspected of needing longer than 2 weeks of circulatory support and if the support is intended as a bridge to transplant. As ECMO has become safer, it is generally agreed that mechanical support should be initiated early before circulatory collapse to avoid prolonged periods of low cardiac output state (LCOS) and organ hypoperfusion. Patients with cardiac dysfunction after cardiopulmonary bypass (CPB) have a better prognosis when ECMO is initiated in the operating room (OR), rather than waiting for deterioration in the pediatric intensive care unit (PICU). In one study of 81 children, those placed on ECMO in the OR had a survival rate of 64%, whereas those put on ECMO in the PICU had a 29% recovery [14]. Pediatric patients who failed to wean off CPB requiring ECMO are a high-risk population with a mortality of 55% [15].

Box 37.1: Indications for mechanical support in neonates, infants, and children

Indications related to cardiac surgery
- Preoperative stabilization and support
- Postoperative support
  - Failure to wean from cardiopulmonary bypass
    - Low cardiac output state
    - Respiratory failure
    - Severe hypoxemia (occluded shunt or right-to-left shunt)
    - Cardiac arrest

Indications unrelated to cardiac surgery
- Respiratory failure (oxygenation and/or ventilation failure)
- Septic shock
- Cardiovascular indications
  - Myocarditis
  - Cardiomyopathy
  - Intractable arrhythmias
  - Instability during cardiac catheterization
  - Pulmonary hypertension
  - Intoxicants
  - Bridge to organ donation
  - Cardiac arrest

Preoperative stabilization and support

Occasionally, neonates with severe cyanosis or cardiogenic shock require preoperative mechanical support for stabilization before cardiac surgery. There are many case reports of successful use of ECMO in this context [16]. At Royal Children's Hospital and Texas Children's Hospital, we have numerous successful anecdotal examples of preoperative ECMO use. At the Children's Hospital, Boston, a retrospective review over 13 years demonstrated the use of ECMO in 26 patients with acute cardiorespiratory deterioration and unrepaired congenital heart disease (CHD) as a bridge to palliative or definitive surgery. Sixteen out of 26 patients survived to discharge. [17] Despite no studies showing superiority of this approach, it is reasonable to conclude that preoperative ECMO may be a useful rescue modality to allow cardiopulmonary and other end-organ recovery as well as a bridge to surgery. Specifically, however, it is noted that neonates with obstructed total anomalous pulmonary venous return (TAPVR) are poor candidates for this approach as the pulmonary pressures remain unacceptably high despite mechanical support and surgery should be performed promptly [17, 18]. Despite this, however, preoperative ECMO can still be lifesaving in patients with obstructed TAPVR.

Failure to wean from CPB or LCOS after cardiac surgery

Failure to wean from CPB after congenital heart surgery is the most common cardiac indication for mechanical support and it is estimated that 2–5% of all children require ECMO after congenital heart surgery [4, 19]. Extracorporeal cardiac life support may be required after CPB due to an LCOS, respiratory failure or severe hypoxemia (due to right-to-left shunt or occluded systemic-to-pulmonary artery shunts). The etiology of an LCOS after CPB may be anatomical (and must be excluded by echocardiography or sometimes catheterization), ventricular dysfunction (often due to long CPB and cross-clamp times), arrhythmias, or PHTN [20]. Mechanical support could be required immediately on attempted separation from CPB or may be required later and used as rescue in intensive care. If mechanical support is initiated in the OR, the cannulas are often placed in the right atrium and aorta via the sternotomy.

Criteria for considering ECMO or VAD in patients with LCOS include a progressive increase in inotrope or vasopressor dosage with evidence of poor end-organ perfusion, such as reduced mixed venous oxygenation <40%, reduced cerebral saturation (>20% below baseline), oliguria, or metabolic acidosis with increasing lactate. Again, initiation of early mechanical support in these situations shows better outcomes [9].

Patients with single-ventricle physiology or cyanotic heart disease are more likely to require mechanical support after CPB. According to the ELSO registry 2015, the most frequent CHD requiring ECMO in neonates is hypoplastic left heart

syndrome (HLHS), with 33% survival of stage 1 palliation surgery, although generally those who require ECMO for hypoxia (often an occluded shunt) have a better outcome than those who require support for low cardiac output [21]. A recent systematic review and meta-analysis of ECMO after CHD repair showed the most common reason for ECMO was left ventricular (LV) dysfunction with LCOS. About 60.3% were able to wean from ECMO and the overall in hospital mortality was 56.8%. Single-ventricle physiology and renal failure were the only independent risk factors for in-hospital mortality [22].

Resuscitation of cardiac arrest

Resuscitation of children with ECMO during CPR for cardiac arrest was first described in 1992. del Nido et al. reported on the use of veno-arterial ECMO (VA-ECMO) for 11 children with a witnessed sudden cardiac arrest [23]. Ten out of 11 patients were centrally cannulated, and seven patients survived to hospital discharge. Using extracorporeal support for management of cardiac arrest is termed "extra-corporeal cardiopulmonary resuscitation" (ECPR). Rapid VA-ECMO for patients suffering in-hospital cardiac arrest (IHCA) has been used increasingly in pediatrics since then [18, 24, 25].

The American Heart Association (AHA) 2010 resuscitation guidelines state, "There is increasing evidence that extracorporeal cardiac life support (ECLS) can act as a bridge to maintain oxygenation and circulation in selected infants and children with cardiac arrest if they are transplant candidates or have a self-limited or treatable illness" [24]. When compared with CPR alone, it appears that ECPR improves survival by 12–23% in children [26]. This is consistent with a multivariate analysis of an observational registry study which showed higher rates of survival to hospital discharge for those managed with ECPR [27]. From analysis of the same registry, ECPR was associated with better neurological outcomes in patients with IHCA of any etiology [28]. After longer-term follow-up, overall, about one-third of pediatric patients have good neurobehavioral outcomes 1 year after ECPR for IHCA [29]. The AHA pediatric resuscitation guidelines of 2020 recommend "ECPR may be considered for pediatric patients with cardiac diagnoses with IHCA in settings with existing ECMO protocols, expertise and equipment" [25, 27, 28]. ECPR is typically only effective when arrest occurs in a highly monitored environment (such as the intensive care); the AHA cautions that there is insufficient evidence for or against for the use of ECPR in out of hospital cardiac arrest or IHCA in patients with noncardiac disease [25]. The AHA (2010) states that there is no good evidence for an upper limit as to the length of CPR after which ECPR should be considered futile; it is known that long-term survival is possible after >50 minutes of CPR [30].

A recent review of the ELSO registry for term and premature neonates receiving ECPR from 1998 to 2010 revealed 39% survived to discharge, however, gestational age, corrected gestational age, and birth weight correlated inversely with stroke and death. Of those born before 34 weeks, the survival was 21%. As expected, if dysrhythmia was the primary diagnosis, the odds of death were significantly lower than those with single-ventricle physiology. Overall, the survival rate was like that of older children receiving ECPR [31]. The April 2021 ELSO report also revealed an overall 42% survival to discharge or transfer in neonatal and pediatric patients receiving ECPR [21]. Chapter 25 presents more information about cardiac arrest and resuscitation in CHD.

Respiratory failure and lung transplantation

When considering mechanical support for respiratory failure, neonatal patients are typically differentiated from (older) pediatric patients due to different etiologies and pathophysiology. With neonates, the conditions requiring ECMO are either acquired at birth or congenital in origin, such as meconium aspiration, pulmonary hypoplasia (possibly with congenital diaphragmatic hernia (CDH)), pneumonia/septicemia, and persistent PHTN of the newborn [32]. Of these neonatal causes, CDH and meconium aspiration syndrome (MAS) are the two most common reasons for the use of ECMO. The specific criteria for ECMO in neonates with respiratory disease vary depending on etiology and on location of providers [33, 34]. However, the general principle is to refer for ECMO due to failure to improve on optimal medical management (lung protective strategies, pulmonary vasodilators, surfactant, and high-frequency ventilation) and the desire to avoid ventilator-associated lung injury. The optimal timing, however, may be difficult, since ECMO is no longer seen as a last-ditch attempt, so that, intervention is aimed at reducing morbidity as well as mortality [35]. Outcome is dependent on multiple factors, including etiology and underlying associated conditions; the 2016 ELSO registry suggests that neonates with CDH requiring ECMO have a 51% survival whereas those with MAS requiring ECMO have an overall 94% survival [4, 35].

The use of ECMO in the neonatal population decreased in the 1990s due to advances in ventilation strategies (including high-frequency oscillation) and medical management, such as nitric oxide (NO) [36]. However, the rate of ECMO use for persistent PHTN and CDH has remained steady. Currently, in total, approximately, 800 neonates require ECMO support annually [4].

Older pediatric patients require ECMO because of acquired conditions, such as pneumonia (bacterial, viral, or fungal), aspiration, acute respiratory distress syndrome (ARDS), or acute respiratory failure from other causes [4]. Of these, infection is the leading cause of respiratory failure requiring ECMO [37]. Today, many pediatric patients requiring ECMO have significant comorbidity, such as renal, lung, and heart diseases. In an ECMO registry review, 19% of these patients had comorbidities in 1993, compared with 47% in 2007 [38]. Because of a lack of randomized controlled trials, the use of ECMO as a treatment modality has been slowly accepted, and recent evidence demonstrates accelerated interest from new advances in equipment/technique [39]. For example, veno-venous cannulation has reduced the need for carotid puncture and therefore reduced the risk of neurological complications [38]. Veno-venous ECMO (VV-ECMO) has had a higher survival to discharge compared with VA-ECMO [37]. During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a minority of pediatric patients with multisystem inflammatory syndrome in children

(MIS-C) required ECMO support. A systematic review of reported cases fulfilling the WHO criteria of MIS-C showed that the need for ECMO was 4% in 783 patients [40]. The ELSO supports the early use of VV-ECMO in ARDS due to SARS-CoV-2 in patients that other measures have failed, especially prone positioning [41].

Technically, ECMO could be used as a bridge to lung transplantation; however, long waiting times on ECMO are associated with morbidity and mortality from bleeding at the cannulation or surgical entry sites, hemolysis and coagulopathy, sepsis, and multiorgan failure. It is known that the survival of pediatric patients having ECMO as a bridge to heart transplant is significantly better than for lung or heart–lung transplant [42]. ECMO is therefore not favored for long-term use as a bridge to lung transplant. New machines, such as the pumpless lung assist devices (described later) may alter the risk–benefit assessment of mechanical support in these patients. After lung transplant, patients who develop primary graft dysfunction may require extracorporeal support. Both VV-ECMO and VA-ECMO can be used, allowing the lungs to recover from the acute injury with an overall rate of survival to discharge of 42% [43, 44].

Sepsis

The updated definition of sepsis in adults is "life threatening organ dysfunction caused by a dysregulated host response to infection" and the definition of septic shock is "a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality" [45]. The definition of sepsis in children is currently being re-examined, but is likely to include risk factors, clinical criteria, and illness severity scores to identify those at high risk of developing sepsis-associated organ dysfunction and mortality [46]. In the meantime, the old definition of severe sepsis is being used in children and refers to the presence of organ dysfunction, hypoperfusion, or hypotension [47].

Sepsis is one of the leading causes of mortality and morbidity worldwide and severe infections kill more than 4.5 million children every year [48]. In Australia and New Zealand from 2007 to 2013, invasive infections, sepsis, and septic shock were responsible for 765 (26·4%) of 2,893 pediatric deaths in ICUs [48]. Overall mortality for invasive infections was 3.9%, sepsis was 5.6%, and septic shock was 17%. Identification of those children at highest risk of mortality is therefore of paramount importance.

Septic shock may be the primary reason requiring mechanical support, or sepsis could be a coexisting problem in a patient with respiratory or cardiac failure. This causes classification difficulties, which can pose a problem for extracting meaningful outcome data. Despite this, sepsis was historically considered a contraindication for ECMO; however, it is now accepted that ECMO is a viable therapy in neonates and children. In neonates, the survival rates are over 80%, whereas, in older children, it is lower, but it has improved lately to 75% for refractory shock and 90% for refractory pneumonia [49]. A recent systematic review of ECMO in children with sepsis was consistent with this whereby overall pooled survival was 65% with neonatal survival the highest group at 73% [50]. Gram-positive organisms were the most common among those requiring ECMO, although many underlying bacterial, viral, and fungal organisms can be implicated [51].

More recently, a sepsis mortality prediction model has been used to assess the effectiveness of VA-ECMO in pediatric septic shock; in patients with a predicted mortality higher than 47.1%, the measured mortality was reduced by 16.1%, whereas in patients with a lower predicted mortality had a higher measured mortality by 16.8% [51, 52]. Some questions remain unanswered from this study, for example, the mortality prediction tool did not consider the different hemodynamic profiles of sepsis in children [53]. In addition, the mode of ECMO was not consistent; 71% provided central ECMO with higher flows compared with 29% with peripheral ECMO. There is some evidence that there is survival benefit from using ECMO with higher than 150 mL/kg/min flows [54]. The American College of Critical Care Medicine has issued a consensus statement on the management of children with septic shock, suggesting that ECMO be considered when a child is deteriorating from hypotension, rising lactate, or progressive multiorgan dysfunction despite high doses of vasoactive/inotrope medications, aggressive fluids, and appropriate medical management [50]. During this assessment, the rate of progression of shock with associated physiological decline is more important than the absolute amount of inotropic support [47].

Myocarditis, cardiomyopathy, and cardiac transplantation

In children without CHD, viral myocarditis is the commonest cause of acute heart failure. ECMO is the initial modality of choice for MCS, because of ease of application, biventricular support, and relatively few complications [55]. Once on mechanical support, ECMO can be used as a bridge to VAD, transplant, or recovery. ECMO in this population was first reported in 1999 with an 80% survival [55]. In the 2016 ELSO registry report, the survival rate for myocarditis requiring ECMO was higher than CHD in neonates and children [4]. Pediatric patients with myocarditis have the highest survival rate of 76%.

ECMO is also used in children with dilated or restrictive cardiomyopathy to BTT. Although VA-ECMO has traditionally been the standard management strategy for myocardiopathy, several reports have shown better survival with VAD [56]. In a prospective, multicenter, single-group cohort study, children who underwent implantation of the Excor® Pediatric VAD as a BTT were compared with a historical control group of children who received circulatory support with ECMO [57]. The patients supported with VAD had longer survival rates than those supported on ECMO but with a high incidence of complications (e.g. bleeding, infection, and stroke). Of note, children who are on ECMO at the time of listing for cardiac transplant have a worse outcome (50% 12-month survival) compared with those on a VAD at listing (76%) [58].

ECMO is also used for patients with early and late ventricular dysfunction after cardiac transplant. In a retrospective chart review of 100 pediatric orthotopic heart transplant recipients, 15 patients required 17 episodes of ECLS. Ten of these episodes were early (<1 month after transplant), and

seven were late (>1 month). Of the 10 with premature graft failure, 8 were weaned from support with graft function recovery, 1 was retransplanted, and 1 died [59]. Late failure was due to acute rejection and had a 50% mortality. ECMO is usually the initial mode of support because of the speed of application and familiarity, as well as the ability to manage circulations with right ventricular (RV) dysfunction and high pulmonary vascular resistance (PVR) [42]. Recently, the temporary use of LVAD support via miniature axial flow pumps (Impella®) solo or combined with VA-ECMO has been successfully used after cardiac allograft failure due to acute rejection [60].

Arrhythmias with hemodynamic compromise

Short-term mechanical support for malignant arrhythmias is a temporizing measure while medical management is optimized, or ablation performed. Etiology includes postcardiotomy arrhythmia, myocarditis, or coronary ischemia. Most patients had supraventricular tachycardia (69%) that needed mechanical support to stabilize. Thirty-three percent underwent transcatheter ablation while on ECMO, while the rest received medical treatment. The long-term survival was 59% [61].

Cardiac catheterization instability

Improvement in skills and equipment has led to a significant number of younger, sicker patients presenting for complex interventional procedures in the catheterization laboratory. ECMO has been used as rescue therapy after a critical event (e.g. failure to wean from bypass, cardiac arrest, severe cyanosis) or prophylactically to manage an LCOS. A single-center 15-year retrospective review found the most common indications for cardiac catheterization while on ECMO were purely diagnostic, atrial septostomies, and stenting of vessels or shunts [20].

Patients at greatest risk include those <1 month of age with poor cardiovascular performance. Four high-risk hemodynamic variables include: high end-diastolic pressure, low systemic arterial saturations, low mixed venous saturations, and high pulmonary artery pressures [62]. In one reported series, 57% of children receiving ECPR in the catheterization survived to discharge [63].

Pulmonary hypertension

Three groups of patients with PHTN candidates for ECMO support. The first group is perioperative patients with reversible PHTN, for example, neonates with total anomalous pulmonary venous drainage that PVR will improve with time after surgical correction. The second group is the severe PHTN patients at high risk of an acute pulmonary hypertensive crisis from intervention or intercurrent illness. Before the PHTN crisis, the suitability of rescue ECMO is discussed. Even centers with an expert mechanical support team report low survival with ECPR in these patients [64]. The third group includes patients with severe medically refractory PHTN who require VA-ECMO as a bridge to heart–lung or lung transplant; however, the likelihood of survival with this approach is quoted as "minimal" and should be made on a case-by-case basis. A recent retrospective analysis of pediatric patients on ECMO with PHTN allowed the development of mortality models. The pre ECMO poor prognostic clinical features are (age <6 months, age >5 years, absence of pneumonia, and pH <7.12). The ECMO-related poor prognostic markers are ECPR, neurological complications, pulmonary hemorrhage, renal replacement therapy, and metabolic acidosis [65].

Novalung® (Novalung GmbH, Hechingen, Germany) has recently developed a paracorporeal pumpless interventional lung assist device that uses a low-resistance hollow-fiber oxygenator. This device has been applied to patients with cardiogenic shock from PHTN, with cannulas placed via sternotomy in the pulmonary artery and left atrium. High pulmonary pressures drive the blood through the oxygenator, without the need for a mechanical pump, removing CO_2 and improving oxygenation. Pulmonary pressures are reduced, which offloads the failing right ventricle, potentially allowing RV recovery [65]. Most of the research with this device has been in the adult population, but there is a need for application in pediatrics.

Intoxicants

ECMO can support both adults and children who have severe toxin exposure [66]. A recent literature review identified 46 reports from 1996 to 2012 where ECMO rescued adult and pediatric patients with ARDS or circulatory shock from poisoning. The most common intoxicants cited were beta-blockers and calcium channel blockers. However, other drugs mentioned were ibuprofen, tricyclic antidepressants, colchicine, and chloroquine. A recent retrospective review of the ELSO registry identified 28 children who required ECMO due to toxin exposure. The in-hospital mortality was 32%. The following features were associated with higher mortality: preECMO use of NO, lower pH, elevated pCO_2 or inotrope requirement while on ECMO [67].

Mechanical support to assist organ donation

There is a worldwide shortage of organs, and significantly fewer cadaveric donors exist for any given child when compared to adults [68]. ECMO provides the potential to improve organ perfusion and increase the availability of viable organs suitable for transplant. Small case series in adults and adolescents have been reported [69].

Cultural, religious, and legal barriers differ depending on the country. ECMO could represent a violation of donor autonomy [70]. However, ECMO has been supported in this setting by ethicists and theologians [71]. Mechanical support improves viable organ retrieval in both brain-dead donors and donation after cardiac death (DCD) [69, 72]. Brain-dead donors supported with ECMO after suffering cardiac arrest or severe cardiovascular or respiratory dysfunction before organ retrieval increase the pool of donors. The timing of implementing ECLS for DCD, before or after the declaration of circulatory death, depends on the institution. The aim is to reduce warm ischemia time and improve the chance of graft survival. Firm conclusions regarding organ outcomes using this technique are challenging to draw in this population at this stage.

KEY POINTS: INDICATIONS FOR MECHANICAL SUPPORT

Mechanical circulatory support should be initiated early before organ injury from a low cardiac output state. Criteria include:

- Progressive increase in inotropes or vasopressors with continued poor tissue perfusion
  - Mixed venous oxygen saturation <40%
  - Cerebral saturation <20% below baseline
  - Oliguria
  - Metabolic acidosis

The American College of Critical Care Medicine states that ECMO should be considered in the treatment of children with septic shock unresponsive to inotropes and fluid management.

Contraindications to mechanical support in children

It is difficult to provide absolute numerical "cut-offs" as to who should categorically not be offered mechanical support. Progressively over the years, the list of absolute contraindications has been shrinking [73]. Contraindications are related to either futility treatment or high risk of death or severe long-term morbidity. As medical equipment and techniques evolve, the risk–benefit balance changes. It is, therefore, wise to consider the suitability of individual patients on their own merits. For example, infants with HLHS were once regarded as inferior candidates for ECLS, but now, this is the most common congenital heart lesion requiring mechanical support of the circulation [74]. A temporizing approach is the "bridge to decision" process for patients with acute circulatory failure. The patient is supported to assess cardiogenic shock and the end or organ damage for 24–72 hours. Thus, transitioning to a long-term MCS device in patients, either transplant candidates or deemed to recover [75].

The futility of mechanical support refers to the presence of a lethal anomaly, either cardiac or noncardiac in origin. Futility includes fatal chromosomal disorders, severe irreversible brain damage, or unrecoverable cardiac or respiratory injury. Of course, "unrecoverable" is patient- and organ-specific, and the definition of futility in the context of ECMO remains very difficult [76].

Malignancy has also been considered under this "futile" category in the past, although the outcome of children with cancer is quite good; however, patients with neutropenic sepsis following bone marrow transplantation have a dismal prognosis. Despite this, a recent report described the successful use of ECMO in a few of these children [77]. Another group considered to be "futile" are those with advanced multiorgan failure. However, McLaren et al. describe 23 children at high risk of death from septic shock, of whom 22 had damage to at least three organ systems. All were cannulated centrally through the chest to obtain higher flow rates, and 17 patients (74%) survived to discharge. This high-flow technique appears to confer more remarkable survival than with conventional ECMO [78].

Neonates pose a particular difficulty in defining contraindications. The ELSO registry shows that neonates have good survival for all diagnoses. However, certain neonatal subsets pose a specific risk when considered for ECMO; data from the ELSO registry indicate overall premature (<37 weeks) neonatal survival from ECMO is 31% compared with 41% in term infants [79]. Survival falls to 19% for neonates <33 weeks of gestational age [79].

Much of the concern with premature neonates and ECMO is because of the risk of developing or worsening intracranial hemorrhage (ICH), i.e. low birth weight, extreme prematurity, and pre-existing ICH. Those with low gestational age (<32–34 weeks) are at the greatest risk. Most bleeds occur in the first 72 hours after birth, so in theory, the risk of ICH and hemorrhage extension may be less after the infant is 3 days old. Grade 3 ICH (blood causing enlargement of the ventricles) and grade 4 ICH (blood extending into the brain parenchyma) confer a poor long-term prognosis [80]. ECMO increases the risk of extension of pre-existing ICH, and most ECMO exclusion criteria include those with ICH grade 3 or 4. Although neonates with ICH < grade 3 have the potential for hemorrhagic extension, it is feasible to manage these patients without worsening their ICH, provided there is imaging and diligent monitoring of their coagulation status [81]. In the absence of good long-term developmental follow-up data, many would currently consider birth weight <1.6 kg as a valid contraindication to ECMO. Regression analysis suggested that 1.6 kg was the lowest threshold weight to achieve a 40% survival in noncardiac ECLS [82]. Although some have suggested ECLS to be beneficial in neonates >32 weeks of gestational age, many consider a gestational age <34 weeks to be a relative contraindication to ECMO. As data emerge, these thresholds change; preterm and neonates <2.5 kg still demonstrate mortality rates after cardiac surgery greater than larger neonates [83]. Examining ECPR in neonates, the survival was 21% for those <34 weeks of gestational age and 20% for those <2 kg. Yet, these findings do not support a strict age cut-off for ECPR [31]. With the above caveats in mind, a list of contraindications is presented in Box 37.2.

Futile treatment in the context of repeated or prolonged ECMO is a problematic issue. The probability of ECMO survival in children with respiratory failure reduces with the number of days on support. We also know that myocardial recovery is rare after 12 days of ECMO support after pediatric cardiac surgery. Despite this, prolonged ECLS has produced

Box 37.2: Contraindications for mechanical support in neonates, infants, and children

Neonatal population

- Severe irreversible CNS injury
- Lethal congenital abnormality (cardiac or noncardiac anomaly)
- Intraventricular hemorrhage grade 3 or 4
- Gestational age <34 weeks
- Very low birth weight, for example, <1.6 kg
- Uncontrollable coagulopathy

Infants and older children

- Severe irreversible CNS injury
- Incurable malignancy
- Advanced multisystem organ failure
- Irreversible organ damage if not suitable for transplantation

CNS, central nervous system.

Note that extreme prematurity and very low birth weight are risk factors for intracranial hemorrhage on mechanical support.

remarkable outcomes in children, so that, delineating "futility" is poorly defined. Therefore, repeat ECMO should not be offered unless the mechanical support was initially withdrawn prematurely or considered a new treatment modality [83]. Poor prognostic features include hyperkalemia in the context of hypothermic arrest. Hyperkalemia indicates irreversible cell damage, potassium leakage, and a poor chance of recovery [84].

Devices

Extracorporeal membrane oxygenation (ECMO)

At Royal Children's Hospital (RCH), our ECMO program began by keeping on CPB overnight patients unable to be weaned. This effort was the last opportunity for the patient to either limp off CPB or die. Unfortunately, most failed to wean and died. Understanding how the ECMO service began gives us insight into where we are now and where we will be tomorrow. Due to the needed change in our service, a small team visited major US pediatric cardiac programs in 1988 and put together a peculiar system that was an adaptation of the CPB machine. The new design used a roller pump, silicone membrane oxygenator with a bladder on the venous line that on collapse would cause an alarm; however, not the pump to stop. The new ECMO system required perfusion bedside 24/7 assistance during all the mechanical support. Later, we modified the ECMO system using a Biomedicus centrifugal pump with pressure monitoring of the venous inlet and arterial outlet. Subsequent, in 1989, Dr Roger B. Mee implanted a modified version of the ECMO system without oxygenator configuring an LVAD in an infant post anomalous left coronary artery from the pulmonary artery (ALCAPA) repair with isolated LV dysfunction who was unable to wean off CPB [85]. The patient was well supported for 7 days and then successfully weaned. This infant was the first pediatric patient assisted LVAD as a BTR. The next step in improving the ECMO system was to adopt centrifugal pumps, which significantly improved their ease of management. However, the high-resistance silicone oxygenator was still an Achilles heel of the circuit requiring high pump revolutions per minute (RPMs) to overcome the afterload. These resulted in high shear forces and cellular dysfunction, which promoted bleeding.

The Pump (Figure 37.1)

Active development of improved centrifugal pumps occurred through the 1990s, with Deutschen Herzzentrum München developing the Jostra Rotaflow, a partially magnetic

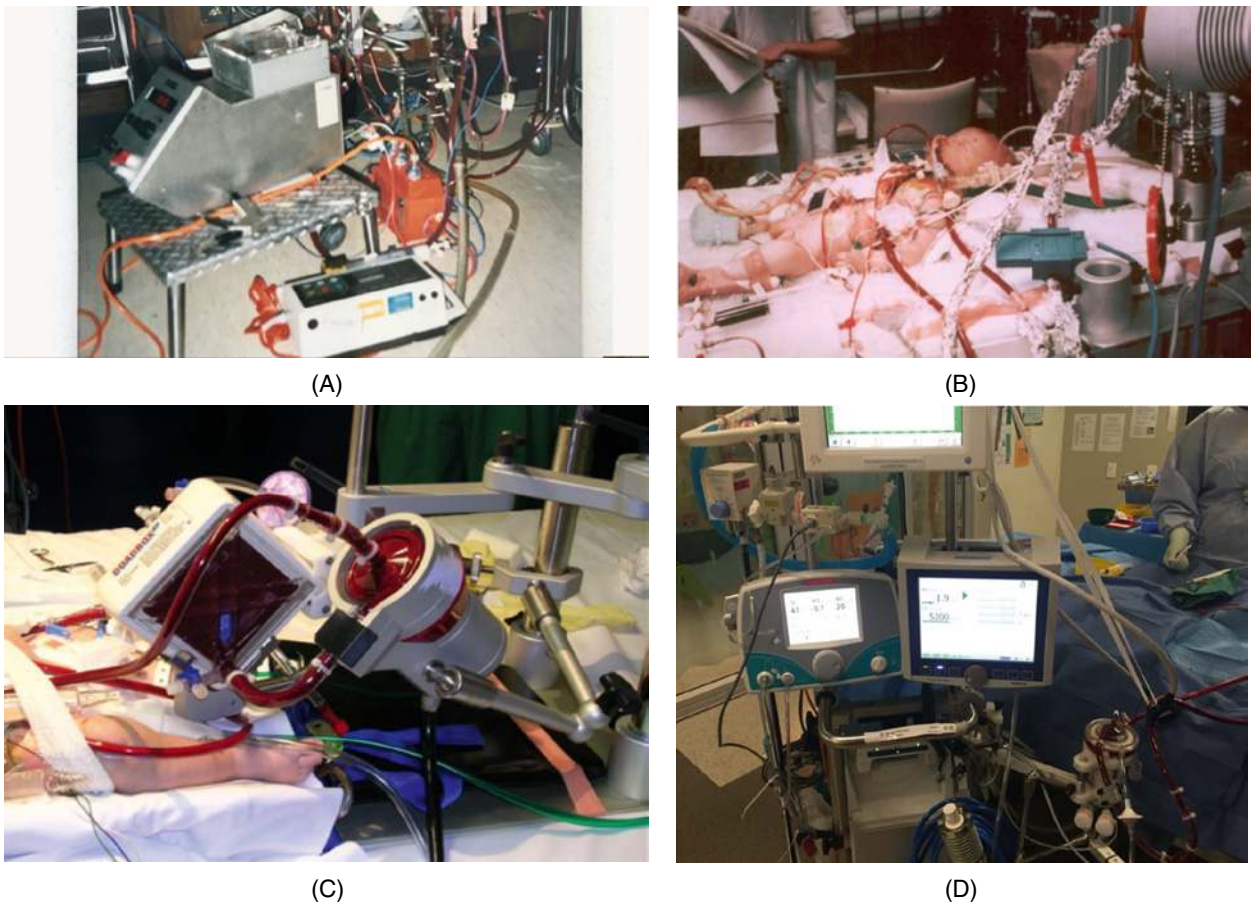


Figure 37.1 (A) First ECMO circuit crafted with a roller pump and a silicone membrane oxygenator; (B) LVAD circuit in an ALCAPA patient using a BioMedicus (Eden Prairie, MN) centrifugal pump; (C) Jostra Rotaflow® (Maquet AG, Hirrlingen, Germany) centrifugal pump with the Quadrox D oxygenator; (D) Medos Deltastream DP3 (Medos Medizintechnik AG, Stolberg, Germany) with the NO delivery system incorporated in the ECMO circuit.

suspended centrifugal pump. This highly efficient device removed the requirement for an axle and seals, which were prone to thrombose and fail after 5 days, such as the Biomedicus Biopump® (Medtronic Corp., Minneapolis, MN, USA). In 1992, a trial comparing the Biomedicus Biopump (Medtronic Corp., Minneapolis, MN, USA) with a conventional roller pump found that the roller pump produced notably more hemolysis [86]. However, by day 5 of use, the Biomedicus acutely begins to cause cell trauma approaching the severity of the roller pump at 7 days. This trial confirmed the clinical experience at RCH of electively replacing the Biomedicus at day 5 as a precautionary measure or earlier if indicated. We adopted the Jostra Rotaflow (Maquet AG, Hirrlingen, Germany) in the late 1990s, which removed the need for elective pump changes. The pump rotor is suspended and driven by a radial permanent magnetic field that stabilizes the impeller in four of the six spatial degrees of freedom. It also allows it to be top-spun on a single blood flushed pivot bearing with minimal load and friction. This pump has a small internal volume, and surface and passage time demonstrate excellent hydraulic efficiency. It can provide 10 L/min of pump flow rate against 400 mmHg of total head pressure, indicating high performance. In long-term ECLS, or prolonged *in vivo* experiments, centrifugal pumps show superior blood handling characteristics if inlet pressures are monitored and do not become excessively negative [87]. Anecdotally, we have found that sub-atmospheric pressures more than –20 mmHg (measured at the cannula) potentiate hemolysis. The concept of integrating a pump and oxygenator into a single device that can monitor core vitals become available for adults as the Cardiohelp system but did not have a pediatric equivalent [88]. The developed pediatric ECMO circuit alternatives were the PediVAS (Levitronix Technologies LLC, Waltham, Massachusetts, USA) and the Medos Deltastream DP3 (Medos Medizintechnik AG, Stolberg, Germany). The PediVAS is a fully suspended centrifugal pump designed as a midterm VAD that some centers in Europe had adopted into their ECMO circuits. However, the disposables were 20 times more expensive than the Rotaflow, which would have created too significant a financial burden in an extensive ECMO program. Our service elected to transition to the Medos Deltastream DP3 (Medos Medizintechnik AG, Stolberg, Germany) oxygenator systems. The entire circuit from Medos was approximately half the cost of the PediVAS pump head, with the potential benefits of being able to provide pulsatile flow with a more sophisticated pump controlling system. Medos provided several oxygenator sizes in a wound polymethylpentene (PMP) fiber configuration. The pump is a diagonal hybrid rotary type that rotates at approximately two times the rate of the Rotaflow to achieve the same flow. Thus, potentially making it more hemolytic if a thrombus occurs on the pump impeller. We undertook a study comparing the hemolysis rate across the three top-performing centrifugal pumps Rotaflow (Maquet AG, Hirrlingen, Germany), Medos Deltastream DP3 (Medos Medizintechnik AG, Stolberg, Germany), and PediVAS (Levitronix Technologies LLC, Waltham, Massachusetts, USA) [89]. The analysis showed no difference between the DP3 and Rotaflow, but the PediVAS fared significantly better causing less hemolysis.

The oxygenator

Several companies released versions of their CPB hollow-fiber oxygenator for ECMO use with the drawback that plasma leaked after several hours, necessitating urgent exchange. The Quadrox D oxygenator adoption finally found a device that could last for most of a potential ECMO run without failing [90]. This device was developed as a low inflammatory activating oxygenator for long CPB runs using a polymethyl pentene plate fiber rather than a spiral wind polypropylene fiber. The pores were logarithmically smaller such that wet out did not occur. Even volatile gases would not cross. The device was exceptionally good at removing even large air emboli; however, the most significant advantage was low resistance, which resulted in immediate improvement of managing anticoagulation, with significantly fewer blood products requirements during ECMO. However, this device was only available for adults, so that, initial use with neonates required a more extensive than necessary oxygenator running at lower than optimal flow, which was still significantly better than the others on the market. To reduce time to support, we also introduced leaving our circuits primed with Plasmalyte® for 4 weeks after ensuring no microbial growth or significant drop in membrane efficiency. Other companies have produced PMP oxygenators, for example, the Medos Hilite® (Medos Medizintechnik AG, Heilbronn, Germany) 7,000 LT (275 mL priming volume), 2,400 LT (95 mL priming volume), and 800 LT (55 mL priming volume). In addition, Medtronic has the Nautilus, while Spectrum is evolving their Quantum platform for ECMO.

Thromboresistant surfaces

The aim is to inhibit activation of the inflammatory and coagulation systems from blood exposure to the foreign surface of the ECLS. To this end, the materials composing circuits either should be inert or hemocompatible. Hemocompatibility refers to those properties that allow ECLS circuits to maintain contact with flowing blood without producing a coagulopathy. Hemocompatibility is related to material's surface, extrinsic conditions (e.g. cannulation sites), blood contact duration, local hemodynamic status (e.g. pulsatile vs. nonpulsatile), flow length, and diameter of tubes). For example, when surfaces feature peaks or valleys (average height or depth = 9 μm), the number of platelets adhering to polyvinylchloride (PVC) surfaces is increased three-fold, compared with polished surfaces [91, 92].

Anticoagulation is challenging, with further improvements still required. Before, we had adopted using heparin-coated technologies in the pursuit of reducing circuit thrombosis, which to our surprise, we found increased with its use. Unfortunately, we used tip-to-tip coating until a patient on VAD support developed a significant thrombus, which resulted in him dying from valve incompetence after several days of successful support. This prompted us to stop using any heparin surface coating and undertake a study investigating potential differences with heparin bonding, only to conclude that postprotamine made this technology prothrombotic [93].

Anticoagulation management has formed the most recent significant advances with less reliance on heparin as the sole mechanism. Since the 2000s, we have used prostacyclin (dose

5 ng/kg/min) as an adjunct and, more recently, NO (20 ppm) into the sweep gas of the oxygenator. These adjuncts have significantly reduced the number of circuit changes per 1,000 hours of ECMO but, more importantly, meant that patients are much less coagulopathic, meaning more stable support [94]. NO and prostacyclin have a synergistic effect on reducing platelet activation from exposure to the ECMO circuit. This reduction in circuit changes results from fewer coagulopathic patients on ECMO, resulting in stable patients requiring fewer interventions.

Ventricular assist devices

The advantages of VAD circuits over ECMO are reduced priming volume from the lack of an oxygenator, shorter tubing, and minor trauma to blood cells. In addition, VADs lessen the ventricular work. VAD circuits are composed of inflow and outflow cannulas, a pump (intracorporeal or paracorporeal), a driving line power source, and a system controller (Figure 37.2) [95, 96]. The inflow cannula attaches to the atrium or the ventricle and transports blood from the left or right heart to the VAD. In left-sided VAD, the outflow cannula connects to the ascending aorta; and in right-sided VAD, the outflow cannula connects to the pulmonary artery. With the optimal placement of inflow cannulas, ventricular cannulas achieve superior unloading of the heart, reducing wall stress, allowing better ventricular recovery, and having a lower incidence of thrombosis. However, endocardial trabeculations can obstruct the inflow cannula in small ventricles (e.g. noncompaction cardiomyopathy). Therefore, these patients may require left atrial cannulation or LV cavity myectomy before ventricular cannulation.

The length of planned support divides VADs into those for short-term use (typically <2 weeks) and those for long-term use (>2 weeks) (Table 37.1, Figure 37.3). They are also classified based on the mechanism that propels blood. For example, ventricular ejection occurs with a rotational device (e.g. centrifugal pumps), a pneumatic pusher plate (e.g. Berlin Heart), or via axial flow (e.g. HeartMate III®).

Impella (Abiomed, Danvers, MA, USA) (Figure 37.4) is a micro axial flow device with three different pump sizes, at 2.5, 5, and 5.5 L/min [97]. The smaller pump provides partial left ventricle support in adults during high-risk cardiac catheterizations (e.g., ablation procedures and urgent catheterizations for acute coronary syndrome). But in pediatrics, this smaller pump can also offer full left ventricle support. The Impella 5 and 5.5 L/min provide full left ventricle mechanical support for adolescents and adults. The main indication is BTR, BTD, or bridge to a permanent support device. The Impella is inserted retrograde through a femoral or axillary artery. The device inlet zone is resting in the left ventricle cavity, where blood is collected and propelled into the aorta. The deployment is performed under direct vision by fluoroscopy and echocardiography. Like many devices initially designed for adults, the Impella will have limited use in younger patients because of its size. The 2.5 L/min pump has a 12 F motor in diameter and requires a 13 Fr peel-away introducer for delivery. Morray et al. in a magnetic resonance

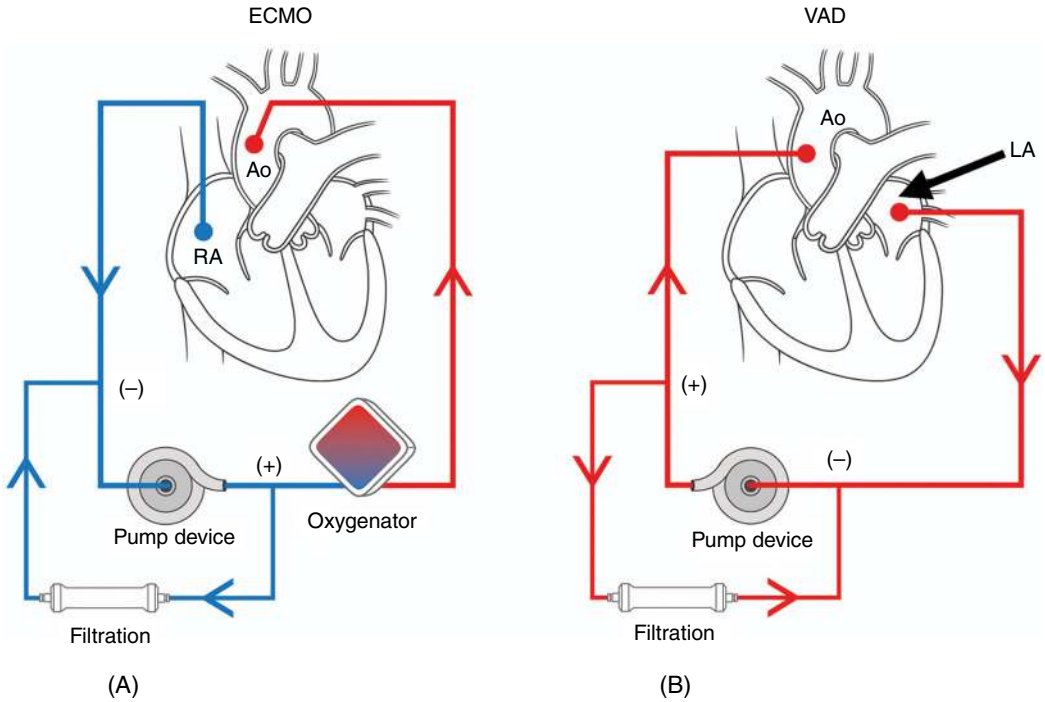


Figure 37.2 Illustration of the (A) ECMO circuit draining deoxygenated blood (negative pressure) from the RA to the pump (positive pressure) through the oxygenator back to the patient through the aortic cannula. Note the ultrafiltration through the venous side beyond the pump; (B) VAD circuit draining oxygenated blood (negative pressure) from the LA to the pump (positive pressure) back to the patient through the aortic cannula. Note the ultrafiltration beyond the pump. Abbreviations: RA, right atrium; Ao, aorta; LA, left atrium.

Table 37.1 Ventricular assist device systems available in the United States

	Pump/flow type	Stroke volume (mL)/ pump speed (rpm)	Flow range (L/min)	BSA range (m^2)	Device type
Short term (<14 days)					
Rotaflow	Centrifugal/nonpulsatile	0–4,500 rpm	0–9.99	No minimum[a]	Rotational
Impella 2.5[b]	Centrifugal/nonpulsatile	0–50,000	0–2.5	>0.9–1.1[c]	Axial
Impella 5	Centrifugal/nonpulsatile	0–33,000	0–5	>1.1[c]	Axial
Impella 5.5	Centrifugal/nonpulsatile	0–33,000	0–5.5	>1.1[c]	Axial
Long term (> 14 days)					
Pneumatic pulsatile ventricular assist devices					
Berlin heart EXCOR	Pulsatile	12, 15, 25, 30, 50, 60 and 80 mL	Variable[d]	>0.2	Pusher plate
SynCardia total artificial heart	Pulsatile	50 and 70 mL	Up to 9.5	>1.7–2.5	Pneumatic-driven chambers
Continuous-flow ventricular assist devices					
HeartMate III	Axial	3,000–9,000 rpm	0–10	>1.4	Axial
HeartWare®	Centrifugal/nonpulsatile	1,800–4,000	0–10	>1.4–2.6	Axial

See text for complete details.

[a] Smaller patient reported 1.9 kg neonate.

[b] 2.5 L/min flow needs a 17 F arterial cannula; 4 L/min flow needs a 15 F arterial cannula.

[c] The Impella is a partial support device which enhances the patient cardiac output – the limitation in pediatrics is the vascular access needed for the size of the cannulas.

[d] Depends on pump size and set rate.

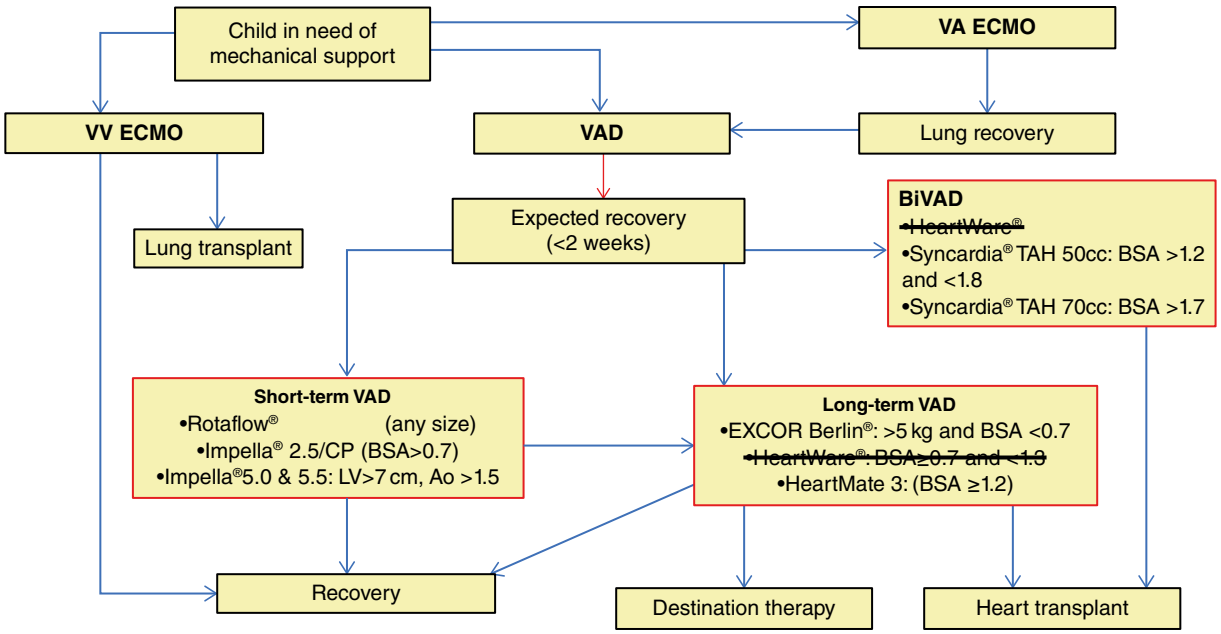


Figure 37.3 Algorithm of MCS used at Texas Children's Hospital. The recall of the HeartWare Ventricular Assist System by the FDA leaves a gap in the patients with BSA ≥0.7 and <1.3. Abbreviation: BSA, body surface area; FDA, Food and Drug Administration; MCS, mechanical circulatory support.

imaging (MRI) and echocardiographic study, define minimum size parameters that are necessary for the correct placement of the Impella 2.5 L/min catheter. The device needs a 7.5 cm LV catheter length achieved when the patient height is 122 cm, the weight of 23 kg, and body surface area (BSA) of 0.89 m^2 [98]. The 5.0 L/min pump is a 21 F motor in diameter, requiring a femoral cutdown for delivery. The 5.5 L/min motor is 18 F in diameter, requiring axillary cutdown. The 5.5 L/min pump does not have a pigtail at the end of the catheter and is shorter (70 vs. 135 cm). Finally, another Impella, the Impella RP, is designed to provide support to the right ventricle. The indication for the Impella RP is to support the failing right ventricle percutaneously implanted RV assist device (RVAD). It is inserted in the femoral vein via a 23-French sheath, and the

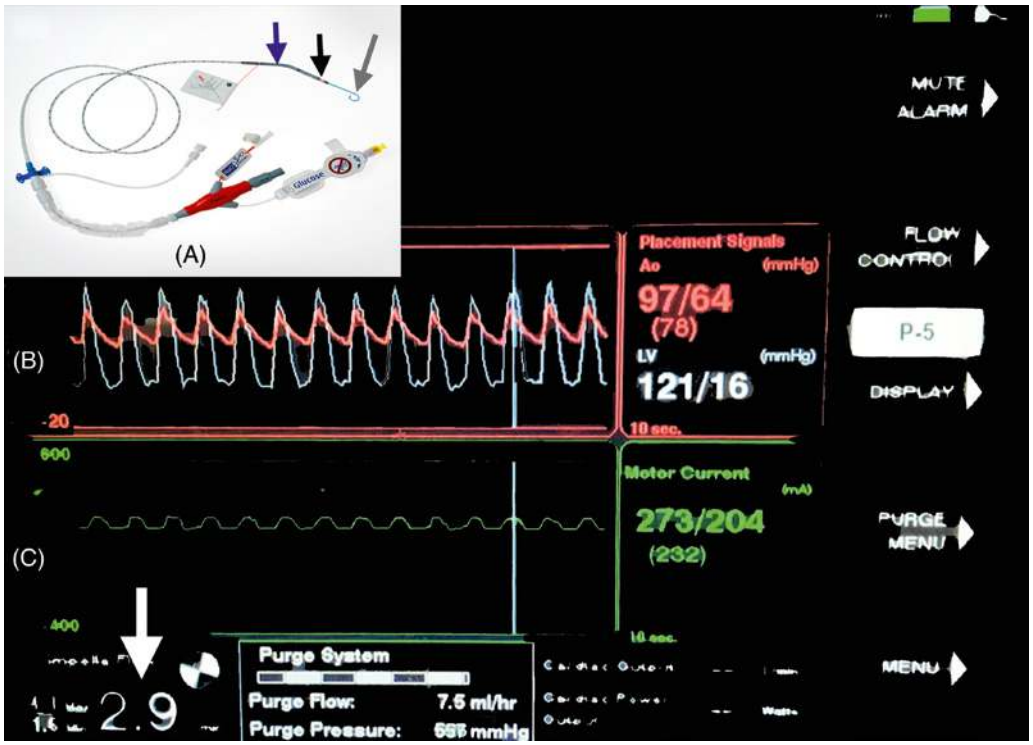


Figure 37.4 (A) Impella 2.5 L/min catheter showing the pig tail end (grey arrow), the blood inlet area (black arrow) and the blood outlet area (blue arrow); (B) Impella console placement signal in red aortic pressure and in white left ventricular pressure; and (C) Green trace showing the motor current in MA, the device flow is 2.9 L/min (white arrow).

motor has a 22 F diameter. Recently, Qureshi et al. published their experience with the Impella RP in adolescents with RV failure reporting an 83% survival to hospital discharge [99].

The Berlin Heart VAD (EXCOR) (Figure 37.5) is a pulsatile, paracorporeal device suitable for all pediatric patients, including neonates [100]. It is available in several sizes (10–60 mL). Most miniature pumps are appropriate to support neonates and infants (weight 3–8 kg), and the 25- and 30-mL pumps will support children weighing up to 20–25 kg. It provides pulsatile flow delivered through a pneumatically driven thin membrane pump. In diastole, blood enters the pusher-plate polyurethane chamber through an inlet valve, and negative pressure aid the pump filling. The blood-filled pump is compressed from an air-filled chamber in systole, creating pulsatile systolic flow ejected through the outlet valve to the aorta. Mechanical valves direct the flow, and there is no direct contact between the pumping mechanical parts and blood. The maximum systolic positive pressure generated is 350 mmHg, and the maximum negative driving pressure is –100 mmHg. High pressures are sometimes needed to overcome the resistance of small pediatric cannulas. The pump allows rates between 30 and 150 beats/min and the systolic time between 20 and 70% of the cycle; these parameters can all be monitored and adjusted on the external driving unit. The blood pump is transparent, allowing visual inspection of filling, emptying, and thrombus formation. The pump exchange is indicated if there is thrombus formation in the pump or cannulas to avoid systemic embolization. The blood-contacting surfaces of the pump, including the polyurethane valves, are covered with Carmeda® bioactive heparin coating to prevent thromboembolic complications. The EXCOR has silicon cannulas with a Dacron covering that works as a biological barrier against ascending infections.

Patients supported with this device often do not require mechanical ventilation; they can eat normally and ambulate, making intensive care unit (ICU) discharge possible [97, 98] The EXCOR can be used for biventricular support using two pumps (right VAD [RVAD] and LVAD) controlled by the same external driving unit. The one prospective trial from the USA comparing the EXCOR with ECMO as a bridge to transplantation showed better survival rates with the VAD than with ECMO in two different BSA cohorts (cohort 1, <0.7 m^2; cohort 2, 0.7–<1.5 m^2) [57]. Unfortunately, the incidence of serious adverse events was high in both groups, including major bleeding (42 and 50%, respectively), infection (63 and 50%, respectively), and stroke (29 and 29%, respectively) [57]. In addition, the need for pump exchanges due to thrombosis was frequent. The higher-risk patients in the US pediatric experience had a smaller size, renal dysfunction, hepatic impairment, and required biventricular assist. ECMO before implantation and CHD was not associated with worse outcomes in this study population. In the German experience with 122 implantations, the overall median duration of support was 63.6 days (range 1–841). Fifty-six (45.9%) were transplanted, 18 (14.7%) patients recovered and weaned, 43 (35.2%) patients died, and five remain on the device. In addition, pump exchange due to thrombus (35 patients) and re-exploration due to bleeding (22 patients) were common complications [101].

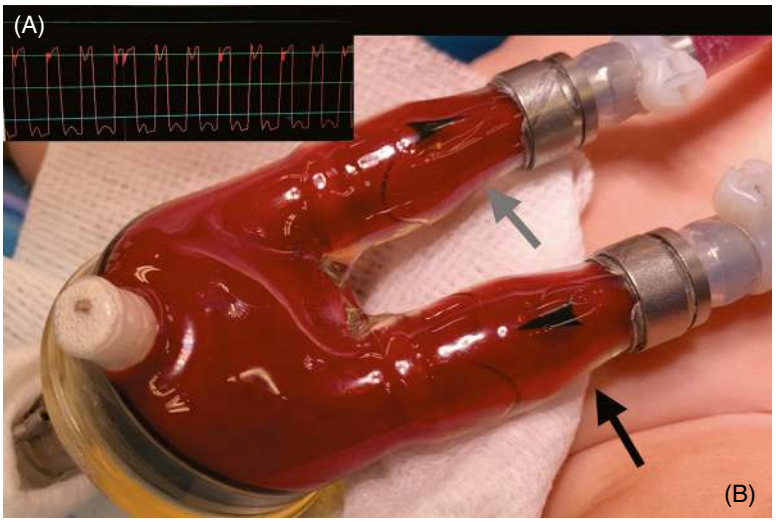


Figure 37.5 (A) Picture of the Berlin Heart console showing: left pump settings (systolic pressure 180 mmHg, diastolic pressure – 30 mmHg, rate 65 bpm and percentage of systole of the cycle 40%). (B) Picture of a Berlin Heart LVAD. The black arrows show the blood entering the VAD from LV (LVAD) and the grey arrow show the blood leaving the VADs to the aorta (LVAD).

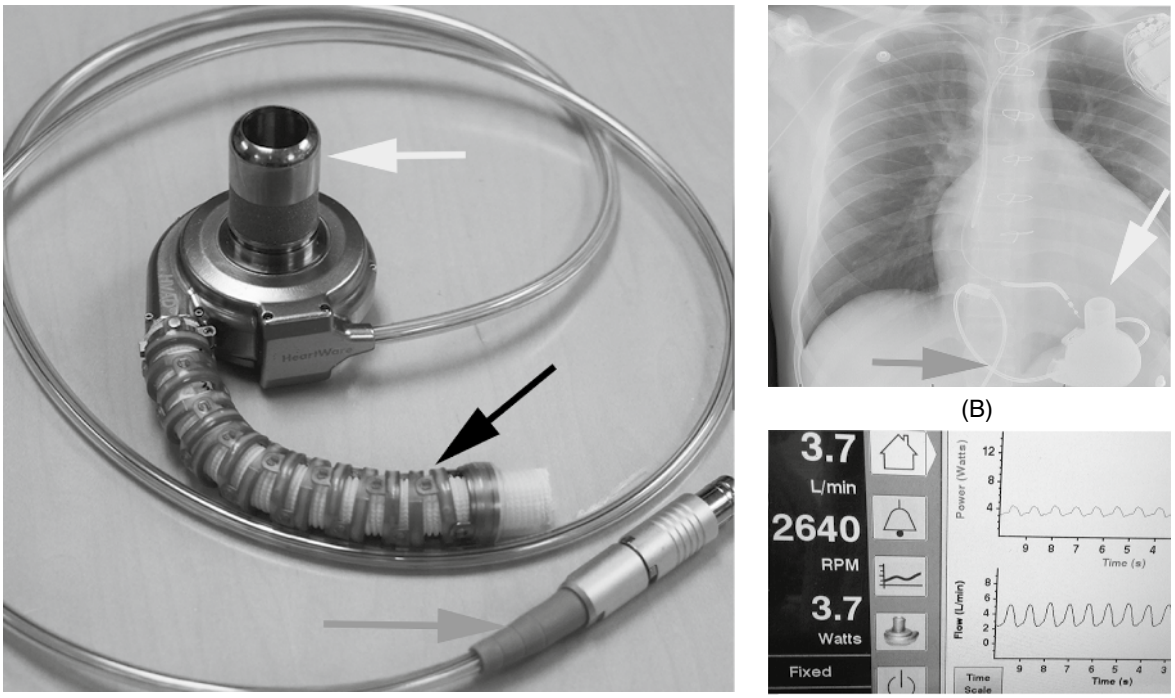


Figure 37.6 (A) Photograph of the HeartWare Ventricular Assist System (total height 58 mm, diameter 49 mm) displaying the drive line (4.2 mm, grey arrow), inlet cannula (diameter 20.5, length 25 mm, white arrow) and outlet cannula (10 mm, black cannula); (B) Postoperative anterior–posterior chest x-ray showing the implanted HeartWare Ventricular Assist System with drive line (grey arrow) and inlet cannula (white arrow), the outlet cannula is not observed because is not radiopaque, in addition an automatic implantable cardioverter defibrillator (AICD) and leads are observed; and (C) HeartWare Ventricular Assist System monitor displaying cardiac output (liter/minutes), device rpm, power (watts) and the graphs (power/time and flow/time).

The HeartWare Ventricular Assist System® (HVAD) (HeartWare, Inc., Miami Lakes, FL) [102] (Figure 37.6) is a small intrapericardial centrifugal flow pump with a rotating impeller, forcing blood through the device using hydrodynamic and centrifugal forces. The displacement volume is 50 mL and can flow up to 10 L/min. The inflow cannula is integrated within the device and is inserted into the left ventricle apex by an adjustable sewing ring – the 10 mm outflow graft anastomoses to the ascending aorta [103]. An external console controls the pump, regulates power, monitors performance, and displays alarms. The pump is connected to the console by a subcutaneous driveline through

the patient's abdominal wall. For safety reasons, two of three different sources power the HVAD: rechargeable lithium batteries, alternating current (AC) power, or a 12 V DC power source. The worldwide experience with the HVAD in 205 pediatric patients (<18 years) showed a low mortality (10.7%) and successful BTT (65%). In addition, a small number of patients (3.2%) recovered function and were explanted. However, right heart support and pump exchange were mortality risk factors [104]. June 3rd, 2021, the US Food and Drug Administration (FDA) alerted the medical community that Medtronic stopped the sale and distribution HVAD system. The recall was due to the increased risk of neurological adverse events and mortality associated with the internal pump. In addition, there is a potential for the internal pump to stop and fail to restart.

The HeartMate III (HM3) (Abbott Cardiac Arrhythmias and Heart Failure, Plymouth, MN) is a new centrifugal VAD characterized by a fully levitated rotor lacking mechanical bearings [105] (Figures 37.7 and 37.8). The HM3 design has a short and wide inflow that decreases shear stress and provides a reliable blood flow pattern supply (Figure 37.8B). In addition, HM3 incorporates a "pulsatility" feature wherein the rotor drops below the set speed and immediately increases above the set speed generating a pulse (~30 cycles per minute). The purpose of "pulsatility" is to allow ejection through the aortic valve reducing stasis and thrombosis. The HM3 insertion is intrapericardial, like the HeartWare® HVAD. Therefore, the modular driveline replacement in the event of malfunction does not need a complete pump exchange. The control screen consists of four boxes displaying pump flow, pump speed, pulsatility index (abbreviated on-screen as pulse index), and pump power. The HM3 allows a wide range of working speeds accomplishing flows between 2.5 and 10.0 L/min. The pump flow is a calculated value. The pulsatility index value is inversely proportional to the support given. The higher the pulsatility index, the lesser the VAD support. The HM3 power ranges between 0.0 and 25.5 W. Five life-threatening warnings display on the system monitor, including pump off, driveline disconnection, low flow × min, low voltage, and no external power. Low-level speed is considered fewer than 3000 rpm. The miniaturized pocket-size controllers and 17 hours battery pack life supports an ambulatory lifestyle. The pediatric experience with HM3 is limited. However, recently O'Connor et al. published the first pediatric HM3 series (40% of the patients < 60 kg), including a few with CHD (mostly Fontan circulation) who presented a low incidence of mortality and adverse events [107]. The smaller patient implanted in this series was 19 kg (BSA 0.78 m^2). There are two limitations to its pediatrics use one is the safest lowest flow (2–2.5 L/min) and the inflow cannula (25 mm) that seats inside the LV chamber [108]. The traditional anticoagulation regime for HM3 includes Coumadin (INR target 2.0–3.0) plus antiaggregation with aspirin (100–200 mg daily). The MAGENTUM 1 trial showed that low-intensity anticoagulation with Coumadin to a lower INR target (1.5–1.9) and aspirin was adequate [109]. The risk

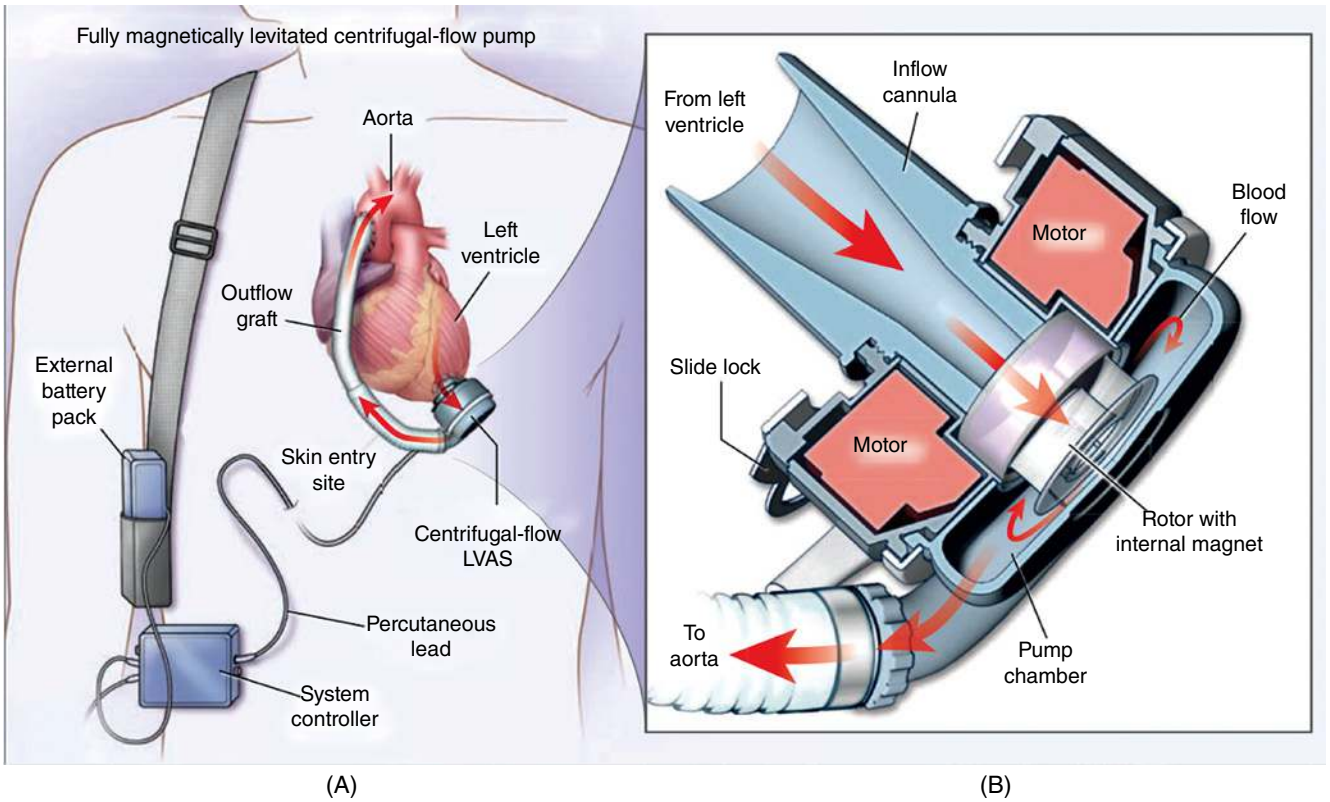


Figure 37.7 Diagrams of the HeartMate III Centrifugal-Flow Pump: (A) shows a diagram of the fully magnetically levitated centrifugal-flow pump with the control system and the external battery pack and (B) illustrates the blood entering the central axis of the rotor and is driven outward centrifugally to the outflow of the pump. Mehra et al. [106]. Reproduced with permission of Massachusetts Medical Society.

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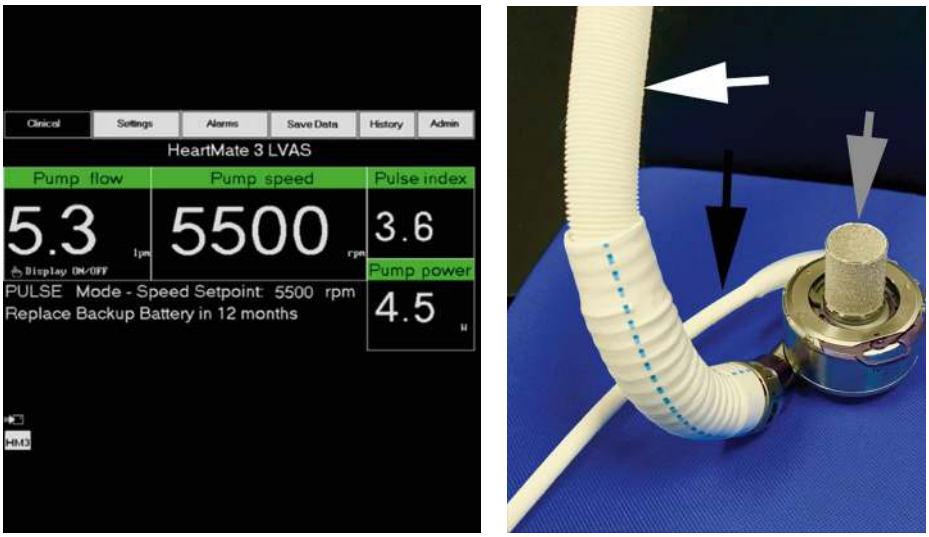


Figure 37.8 (A) Clinical screen showing four parameter boxes at the top of the screen report measured values of pump flow (lpm), pump speed (RPM), pulsatility index (abbreviated on screen as pulse index), and pump power (Watt); (B) picture of the HeartMate III showing the inflow cannula (grey arrow), outflow cannula (white arrow), and the drive line (black arrow).

of thromboembolic complications after the stabilization period (6 weeks) did not increase.

SynCardia Total Artificial Heart. (SynCardia Systems Inc., Tucson, Ariz) (Figure 37.9). It is a pneumatically driven pulsatile biventricular device with two prosthetic polyurethane ventricles (70 mL each) [110]. Each ventricle has two mechanical valves providing unidirectional inflow and outflow from the ventricle. The valves are single-leaflet Medtronic-Hall (Minneapolis, MN), 27 mm for the inlet and 25 mm for the outlet. The SynCardia Total Artificial Heart (STAH) has the most significant inflow, and shortest distance of blood traveled of all available VADs. The large valves and short blood path provide very little resistance, decreasing stasis and thrombosis [111]. The prosthetic ventricles coupled with silicone cuffs to two atrial connectors and two connectors on the end of the grafts sewn to the aorta and pulmonary artery. The external console displays the pressure waveform of each cardiac cycle and has two independent controllers for emergency backup. Compressed air powers the device. Two separate wire-reinforced conduits connected to the right and left prosthetic ventricles. The indication of the STAH are patients unable to be supported by VAD, such as those who require biventricular support or have PHTN (>4.5 Wood units). Successfully used after catastrophic intraoperative heart damage, failing Fontan, refractory arrhythmias, or irreversible cardiac rejection after transplantation have been reported. Pediatric use is limited because the device needs a distance between the sternum and the 10th anterior vertebral body of >10 cm. The recommended BSA is >1.7 m^2, but it has been used successfully in patients with a BSA of 1.5–1.7 m^2. The smaller 50 mL device is recommended for patients with a BSA of 1.2–1.7 m^2 [112]. Morales et al. published the worldwide experience with STAH in 43 patients under 21 years old [113]. Most of the patients were older and received the 70 ml pump. Twenty-five patients (58%) were successfully bridged to transplantation with a mean duration of support of 146 days.

KEY POINTS: DEVICES

- Roller pumps produce a linear increase in hemolysis that is not observed with centrifugal pumps.
- Centrifugal pumps are generally used for short-term ventricular support (less than 2 weeks)
- Impella either percutaneous or surgically has become the most used temporary ventricular assist device
- The Berlin Heart EXCOR device:
  - Has several sizes of pumping chambers versatile in pediatrics
  - Allows patients to be extubated, ambulate, and eat normally
  - Can be used as an LVAD, RVAD or BiVAD;
- HeartWare Ventricular Assist System is currently of the market but is still implanted in several patients
- HeartMate III fully levitated rotor lacking mechanical bearings
  - "Pulsatility" feature wherein the rotor drops below the set speed and immediately increases above the set speed generating a pulse (~30 cycles per minute).
- SynCardia Total Artificial Heart biventricular support or sever pulmonary hypertension (>4.5 Wood units).

Role of echocardiography in mechanical support

Extracorporeal membrane oxygenation

Transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) helps detect complications during ECMO [114]. Before initiating ECMO, echocardiography rules out reversible causes of cardiogenic shock. In addition, it detects anatomic variations that affect cannula insertion in

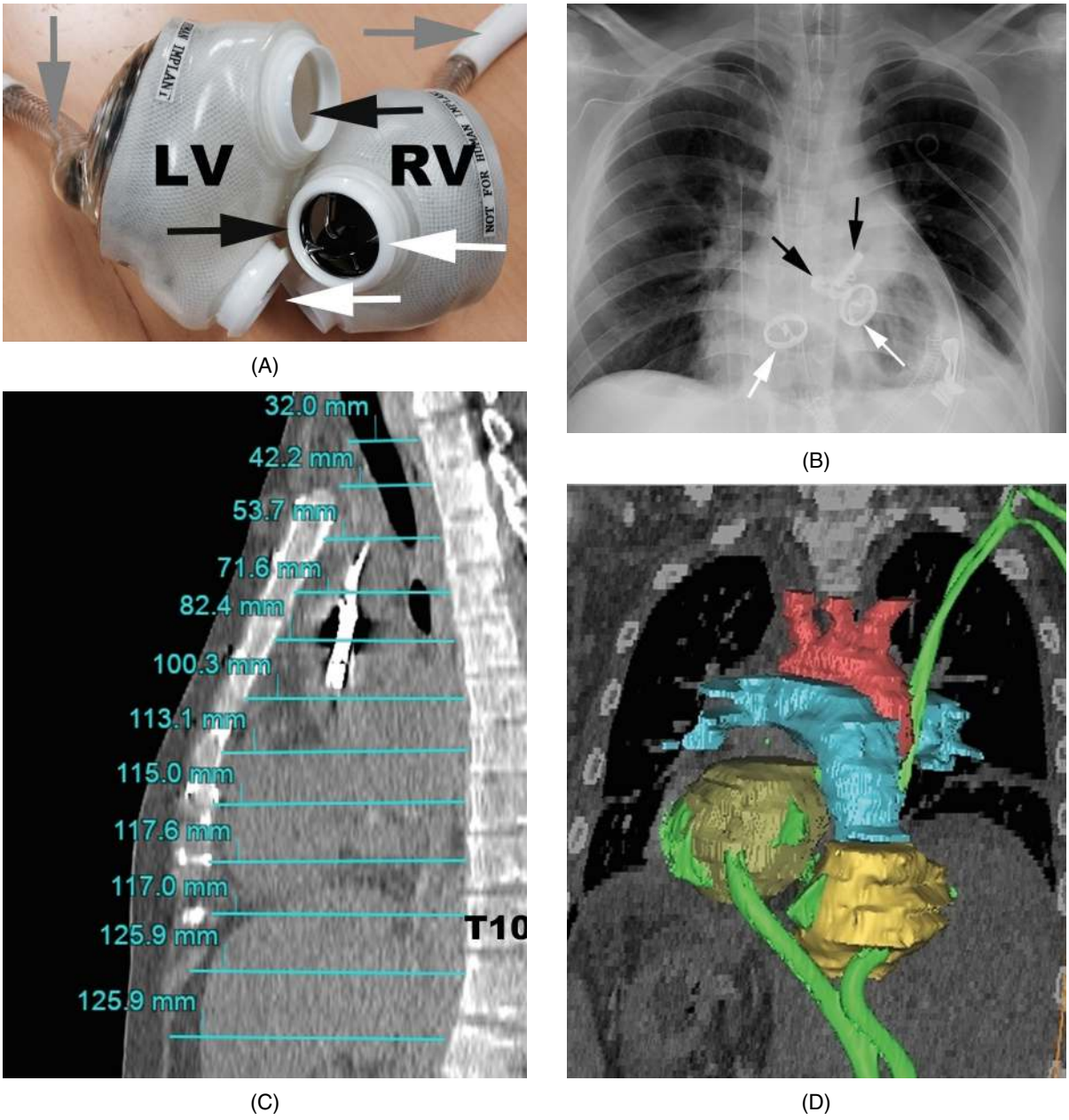


Figure 37.9 (A) Image of the Syncardia TAH showing the LV and RV pump, drive line (grey arrows), inlet valves (white arrows), and outlet valves (black arrows); (B) antero-posterior chest x-ray of an implanted Syncardia TAH displaying inlet valves (white arrows) and outlet valves (black arrows); (C) preoperative chest computed tomography (CT) performed towards placement of Syncardia TAH, the anterior posterior dimensions of the thoracic cavity at T-10 level is 117 mm (minimum for implantation is 100 mm at that level); and (D) preoperative three-dimensional CT reconstruction of Syncardia TAH for surgical implantation exhibiting drive line (green), Syncardia TAH (yellow), pulmonary artery (blue), and aorta (red). Abbreviations: TAH, total artificial heart; LV, left ventricle; RV, right ventricle; CT, Computer Tomography; T-10, 10th thoracic vertebrae.

the right atrium, such as a prominent Chiari network or an aneurysmal atrial septum. If central cannulation through sternotomy is required, TEE is a better choice, as most TTE windows are not available. Kuenzler et al. analyzed the echocardiography of 193 pediatric patients supported with ECMO, detecting a 17.8% incidence of cannula malposition. With echocardiography, the incidence reduced to 3.3% [115]. After the initiation of ECMO, echocardiography assesses the LV unloading and the potential need for left atrial venting via surgical or balloon atrial septostomy [114]. In addition, echocardiography monitors the aortic valve opening because limited aortic ejection increases the risk of blood stasis, leading to thrombosis. Conversely, increasing aortic valve opening during ejection indicates LV recovery when decreasing the ECMO. Echocardiography is used to periodically evaluate cannula positioning and thrombi formation, chamber filling and function, and cardiac compression from pericardial effusion. Tamponade physiology is typically not evident until the patient is off ECMO [116].

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Ventricular assist devices

The American College of Cardiology, AHA, and American Society of Echocardiography consider TEE to be a class 1 indication for the insertion of a VAD (Table 37.2) [116–119]. Before initiating VAD support, TEE is helpful to rule out conditions that jeopardize VAD function. These conditions include mitral stenosis, endocardial trabeculations, and aortic insufficiency. These conditions limit the filling of the device and impede LV unloading. Mitral regurgitation and aortic stenosis do not affect device function. Mitral regurgitation

Table 37.2 Role of transesophageal echocardiography in VAD insertion

Prebypass period	**Tee windows**	**Comments**
Monitor:		
LV size, filling and function	ME4Ch, TGSAX, TG2ch	LVEDD
RV size, filling and function	ME4Ch, MERVIO	Need for RVAD placement RVEDD and L/R ratio calculation
Diagnose:		
Right-to-left shunting (PFO, ASD, VSD)	ME4Ch, MEBC, TGSAX	Causes of severe hypoxemia with LV unloading Agitated bubble study Avoid Valsalva maneuver in patients with marginal physiology
Aortic regurgitation	MELAX, DTG5Ch, DALAX	Increases LVAD preload and LV dimension – impeding LV rest
Mitral stenosis (rare)	ME4Ch, basal TG	Impedes device filling MV commissurotomy
Endocardial trabeculations (noncompaction cardiomyopathy)	ME4Ch, MELAX, TGLAX	Obstruct inflow cannula Resect subvalvular apparatus
Tricuspid regurgitation	ME4C, MERVIO, MEmodBC	Assess the need for TVR Calculate PASP = V_{peakTR}^{2} + CVP
LV Thrombi	ME4Ch, TG SAX	LV thrombectomy before VAD placement
Pulmonary regurgitation	MERVIO, MEAASAX	Rule out before RVAD placement
On bypass period	**Tee windows**	**Comments**
Monitor:		
Cannula alignment		
Inlet	ME4Ch, MELAX	CWD peak velocity <1.2 m/s
Outlet	MELAX	CWD peak velocity 1.0–2 m/s
Deairing	ME4Ch, MELAX	Need for aortic venting Trendelenburg position
Degree of decompression	ME4Ch, TG SAX	Too much LV unloading could shift the interventricular septum causing TF
Diagnose:		
Residual right-to-left shunting	ME4Ch, MEBC, TGSAX	Severe hypoxemia with LV unloading
Rule out aortic regurgitation	MELAX, DTG5Ch, DALAX	Increases LVAD preload and LV dimension – impeding LV rest
Postbypass period	**Tee windows**	**Comments**
Monitor:		
Pericardial effusion / Cardiac Tamponade	ME4Ch, TG SAX	Most common cause of hemodynamic instability and reoperation (20–30%)
Aorta (ascending)	MELAX	Aortic dissection
RV size, filling and function	ME4C, MERVIO	Need for RVAD placement (Transient VS Permanent)
Tricuspid regurgitation	ME4C, MERVIO, MEmodBC	Too much LV unloading could shift the interventricular septum causing TR
Decompression of LV and LA	ME4Ch, MELAX, TGSAX	
Air entrainment	ME4Ch, MELAX	Need for aortic venting Trendelenburg position

Abbreviations: ASD, atrial septal defect; CWD, continuous wave Doppler; DALAX, descending aorta long axis; DTG5Ch, deep transgastric five chamber; LV, left ventricle; LVAD, left ventricular assist device; ME4Ch midesophageal four chamber; MEBC, midesophageal bicaval; LVEDD, left ventricular maximal end-diastolic diameter; MEmodBC, midesophageal modified bicaval; MERVIO, midesophageal right ventricle inflow/outflow tract; PASP, pulmonary artery systolic pressure; PFO, patent foramen ovale; RV, right ventricle; RVAD, right ventricular assist device; RVEDD, RV maximal end-diastolic diameter; TGLAX, transgastric long axis; TGSAX, transgastric short axis; TR, Tricuspid regurgitation; TVR, tricuspid valve repair; V_{peakTR}^{2}, peak velocity of the tricuspid regurgitant jet; VSD, ventricular septal defect.

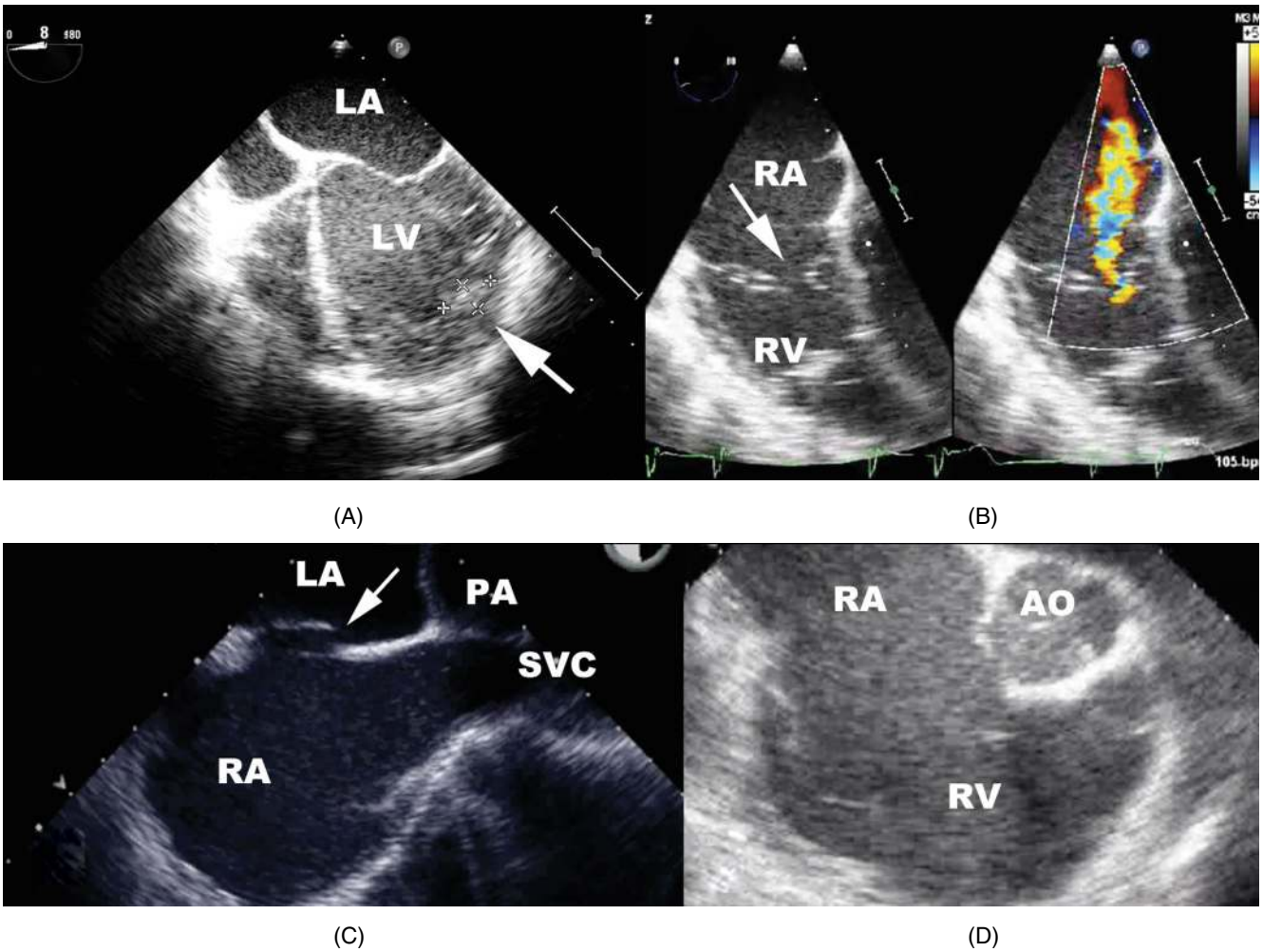


Figure 37.10 Preoperative TEE displaying common procedures performed during LVAD placement, such as: (A) 2-D image at midesophagus four chamber view (0°) on patient with a dilated cardiomyopathy showing a dilated LV with an intra-cavitary thrombus (white arrow) requiring surgical thrombectomy; (B) 2-D and color Doppler images at midesophagus four chamber view (0°) exhibiting an area of noncoaptation (white arrow) and severe TR by color flow Doppler needing TV repair; (C) 2-D image at midesophagus bicaval view (90°) showing a PFO (white arrow) needful of surgical closure to avoid hypoxemia once LVAD support started due to unloading of LV and LA chambers; and (D) 2-D image at midesophagus RV inflow and outflow tract view displaying a severely dilated RA and RV that might require RVAD support in addition to the LVAD placement. Abbreviations: 2-D, two-dimensional; Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium, RV, right ventricle; SVC, superior vena cava; TEE, tranesophageal echocardiography; TV, tricuspid valve; TR, tricuspid regurgitation.

generally improves from LV unloading by reducing left ventricle chamber size and mitral annulus size. Preoperative echocardiography should screen for septal defects (Figure 37.10). Unrepaired atrial or ventricular communications should be closed before VAD insertion. Unloading the left-sided chambers produces significant oxygen desaturation. Echocardiography screens for potential intracardiac thrombi, as thromboembolic events are common and potentially devastating. Intraoperative measures of RV function, such as tricuspid annular plane systolic excursion, tricuspid annular systolic velocity, and RV strain have not been helpful to predict RV failure after LVAD implantation [120]. As RV function commonly has significant improvement from unloading the left ventricle in children. Real-time visualization of RV function should be performed by intraoperative TEE as LVAD support is initiated. Devices placed on CPB should undergo interrogation of the inflow and outflow cannulas before weaning. The inflow should be laminar with a velocity <2 m/s. A peak flow velocity >2.3 m/s along with the turbulent flow indicates inflow cannula obstruction and an indication for surgical revision (Figures 37.11 and 37.12). The normal outflow has a low velocity (peak velocity 1.0–2.0 m/s). Continuous monitoring of RV function and the detection of air is crucial for early intervention. Air may enter through suture lines if the left ventricle completely collapses, and sub-atmospheric intra-device pressures develop. While weaning from CPB, echocardiography determines RV function and guides (RVAD) implantation, if needed (Figure 37.13). Severe septal shifting to the left is an indicator of right-sided heart failure and the need for RVAD. A temporary RVAD can be used when rapid RV recovery is anticipated. Once LVAD support starts and CPB flows decrease, TEE quantifies left ventricle decompression and the degree and direction of movement of the interventricular septum.

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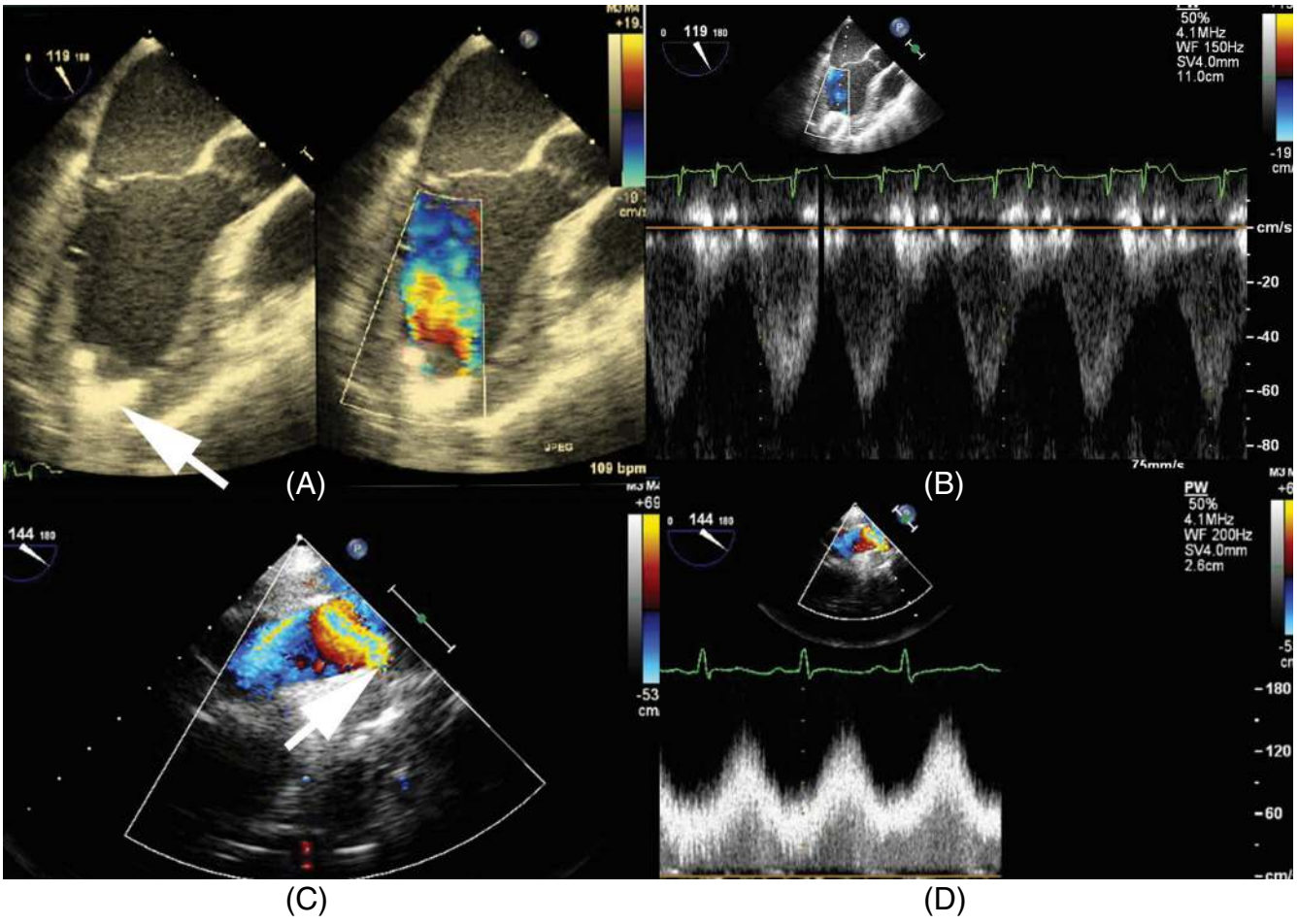


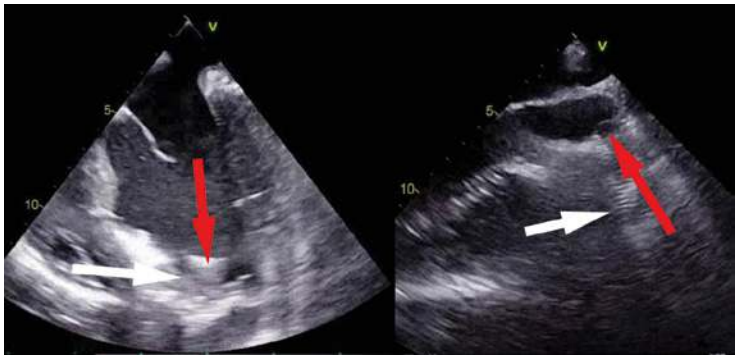
Figure 37.11 Postoperative TEE images showing (A) 2-D and color Doppler images at midesophagus long-axis view (110°) of the HeartWare inflow cannula at the apex of the heart (white arrow); (B) pulse wave Doppler interrogation at the same location showing unobstructed inflow (<70 cm/s); (C) Color Doppler image at the aortic long-axis view (140°) of a HeartWare outflow cannula (white arrow) unobstructed flow is seen in the ascending aorta; (D) pulse wave Doppler interrogation at the same location showing unobstructed outflow (<150 cm/s). Abbreviation: TEE, transesophageal echocardiography.

TEE monitors the interventricular septum shift, sufficient LV unloading and ensures that the aortic valve opens periodically. Aortic dissection distal to outlet cannula insertion site is a potential complication. Finally, after chest closure, a final scan is performed to exclude the possibility of kinking of the cannulas or RV compression. Echocardiography is helpful to guide the percutaneous VAD placement (e.g. Impella) (Figure 37.14) [121]. TEE helps to monitor the correct positioning. In long-axis midesophageal aortic valve view, the device inlet should be 3.5 cm below the aortic valve and the outlet above the aortic valve. In the transgastric long-axis LV view, the device positions away from the mitral valve toward the LV apex. Improper deployment of the Impella includes device too far into the left ventricle (e.g., inlet >3.5 cm from the aortic valve or outlet across the aortic valve), outlet too far into ascending aorta, or pigtail in the subvalvular apparatus of the mitral valve. Echocardiography imaging of the STAH is technically challenging due to artifacts caused by the device and its valves. TEE helps diagnose right-to-left shunting, distortion, and compression of systemic and pulmonary venous return to the native atrium, all of which affect STAH function. TEE also guides the de-airing procedures by imaging the ascending aorta. Once the device is functioning, the Medtronic-Hall valves (tilting disc) in the atrioventricular position can be interrogated to assure adequate function [122].

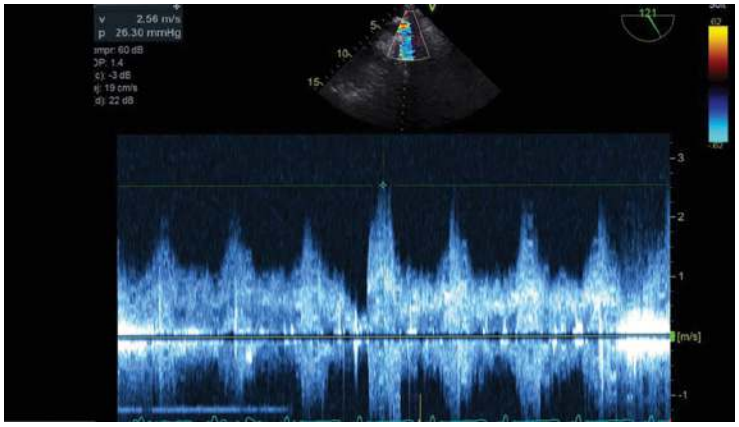
Weaning from circulatory support

ECMO weaning

Patients are weaned from ECMO when their cardiac function recovers, and their lungs can support adequate oxygenation and ventilation using conventional mechanical ventilation. When the myocardium has an acute insult, such as acute myocarditis or ischemia from a prolonged period of CPB, ECMO can usually be weaned 72 hours after the initiation of support. Echocardiographic criteria associated with successful ECMO weaning include LV ejection fraction >35%, LV outflow tract velocity–time integral >10 cm, lack of ventricular dilatation, and no pericardial effusion [123]. In anticipation of ECMO weaning, optimal inotropic support restarts and full ventilation resumes. There is a gradual reduction in the ECMO flow while carefully evaluating the patient's

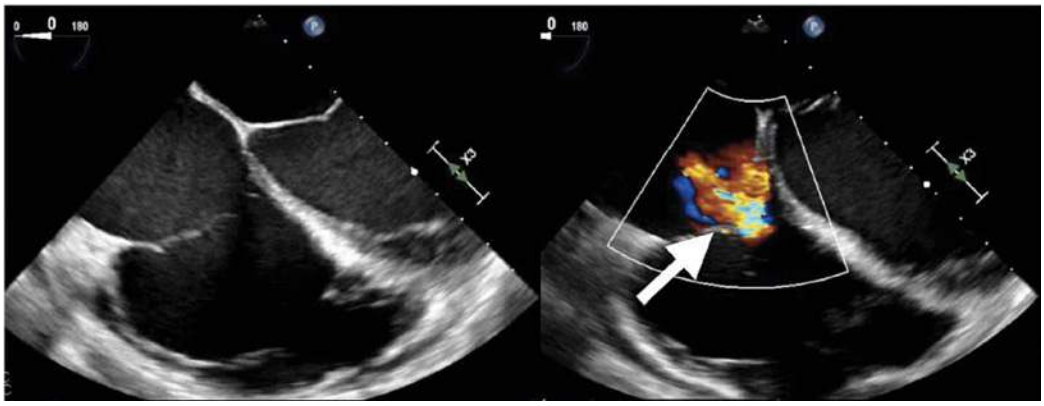


(A) (B)

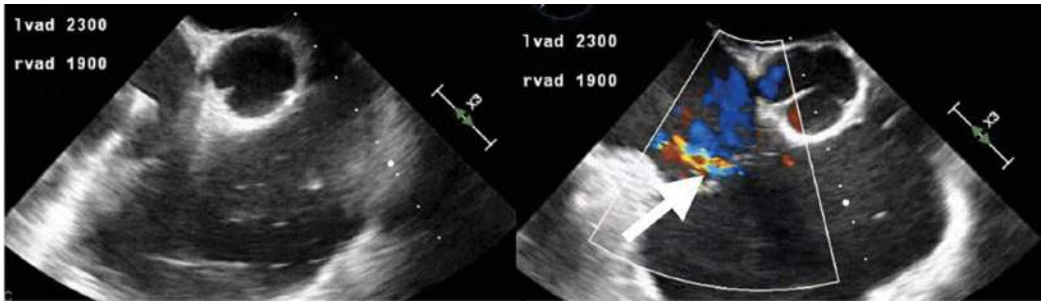


(C)

Figure 37.12 Transesophageal echocardiography of a HeartMate III implantation. (A) Midesophageal four chamber view showing the inflow cannula (white arrow) and the direction of flow (red arrow); (B) midesophageal aortic long-axis view illustrating the outflow cannula in the ascending aorta (white arrow) and the direction of flow (red arrow); and (C) pulse wave Doppler showing an unobstructed outflow cannula (V_{max} 2.5 m/s).



(A) (B)



(C) (D)

Figure 37.13 Transesophageal echocardiography of a patient with dilated cardiomyopathy with biventricular failure: (A) midesophageal four-chamber view showing severely dilated RV with poor systolic function; (B) the same window with color Doppler displaying moderate to severe tricuspid regurgitation in multiple jets (white arrow); (C) midesophageal RV inflow outflow view postbiventricular assist device placement with the RVAD inflow cannula visualized at right atrium (white arrow) and unloaded RV; and (D) the same window with color Doppler showing mild TR (white arrow). Note the LVAD setting at 2,300 RPM and the RVAD at 1,900 RPM.

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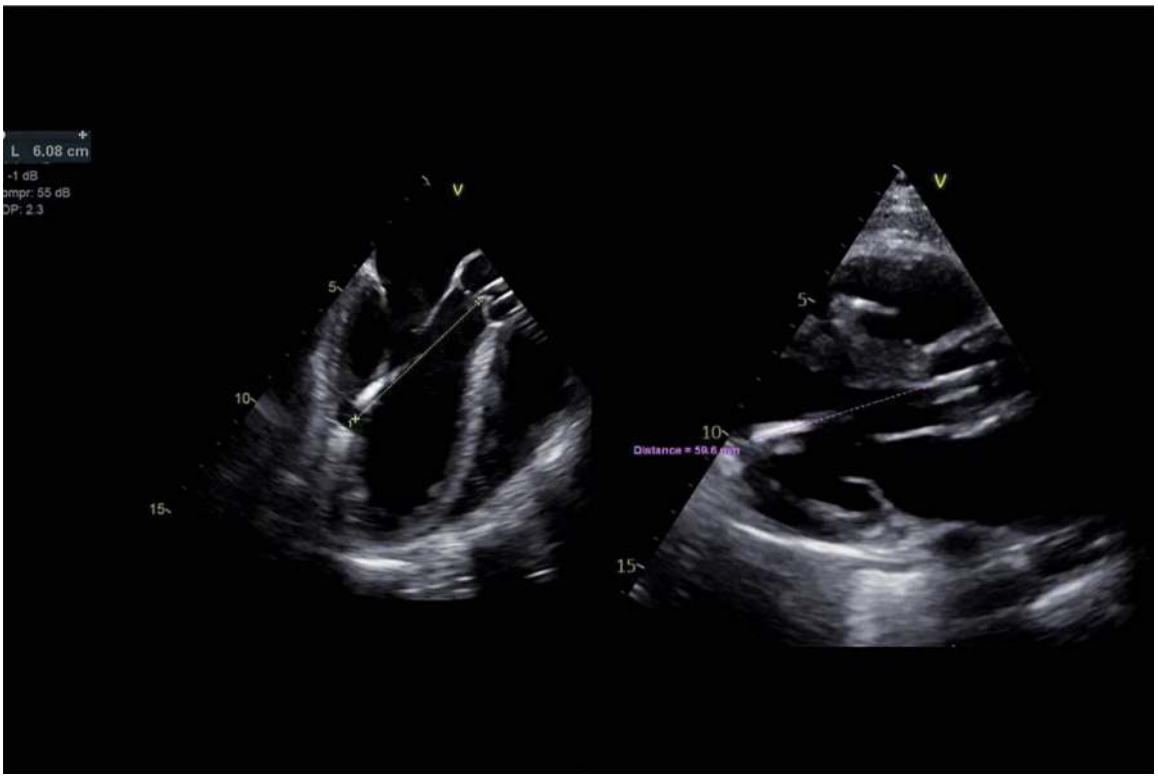


Figure 37.14 Echocardiography images of Impella 5.5 catheter inserted via the left subclavian artery (A) Midesophageal long-axis view with the Impella "motor" positioned against the lateral left ventricle wall below the mitral valve apparatus and papillary muscles. The final distance from the mid-portion of the Impella "motor" to the aortic valve was 6.1 cm; (B) Parasternal long-axis view of the same patient with the Impella motor 5.96 cm below the valve and the outlet in the ascending aorta (white arrow).

hemodynamics (heart rate, blood pressure, arterial waveform, SpO_2, central venous pressure, and pulmonary artery pressure). Tissue perfusion with serum lactate levels and cerebral/somatic oximetry trends. Once flow rates reduce to 25% of full support, a connection (bridge) between the arterial and venous cannulas opens to allow blood to recirculate in the ECMO circuit and avoid thrombosis. The chest is not closed if the cardiac function is marginal after weaning from ECMO until cardiac and pulmonary function recovers [124]. Prolonged cardiac ECMO support (>14 days) and failure to wean from ECMO is associated with high mortality and potential transplant candidates should therefore be transitioned to a VAD when their lung function has recovered, and PHTN controlled [125, 126].

VADs: weaning from CPB to VAD

Intracardiac air complicates LVAD placement. Infield CO_2 insufflation reduces air emboli. However, air can get trapped in the cannulas or the device and is dislodged once the blood flows. Air can have devastating effects if it reaches the coronary or cerebral circulation. As the right coronary artery is the most anterior, it is the most common site for air emboli and will worsen RV function. Therefore, continuous electrocardiogram with ST monitoring and TEE is mandatory while on CPB after ventilation is resumed. De-airing is accomplished by placing the patient in the Trendelenburg position, increasing the mean arterial pressure, and using an aortic vent until all air is removed [127]. Optimal oxygenation and ventilation are mandatory before attempting to wean of CPB. NO decreases the afterload of the RV starting at 20 ppm if there is a concern for RV failure. In addition, the RV function is supported with milrinone (0.375–0.75 mcg/kg/min) and low-dose epinephrine (0.02–0.05 mcg/kg/min). We attempt to maintain a hematocrit of >30% during CPB weaning to optimize oxygen delivery and to anticipate the dilutional effect from other nonred cell blood products transfusion. The CPB flows decrease in a stepwise fashion during the VAD support increase. Pulsatile VAD has a fixed systolic volume determined by the size of the pump, and cardiac output adjusts only by changing the pump rate. Continuous flow VAD output can be increased by increasing the device RPM and modifying the afterload. If VAD is functioning well with favorable hemodynamics, we reverse heparin with protamine. Blood products administration depends on the point of care testing (e.g. ROTEM) and clinical judgment. Careful volume administration to avoid overdistension of the RV. CPB wean is achieved successfully by reducing CPB flows while increasing the LVAD flows and using TEE surveillance of the RV function, LV volume, and the interventricular septal position. With LVAD support, the LV output increases, thereby increasing

Table 37.3 Ventricular assist device troubleshooting[a]

Clinical finding	Echo	Etiology	Treatment
Hypotension	Normal LV chamber filling	Vasoplegia	Stop vasodilators Phenylephrine Vasopressin
	Incomplete LV chamber filling	Hypovolemia[b] (e.g., postoperative bleeding)	Fluid administration
	RV dilation TV regurgitation Incomplete LV filling	RV Failure	Optimize ventilation Nitric Oxide Milrinone ± Epinephrine
Hypertension	Incomplete LV emptying	Increase afterload (e.g., light anesthesia, pain etc.)	Vasodilators Sedation

Abbreviations: CFD, continue flow device; LV, left ventricle; PFD, pulsatile flow devices; RV, right ventricle.

[a] Berlin Heart EXCOR® as a paracorporeal device can be inspected directly.

[b] PFD are more preload sensitive than CFD.

RV function preload. The RV function output depends on the relationship between the RV function compliance, the septal shift, and the RV function afterload. Ideally, one observes improved RV function after the left ventricle is supported and the pulmonary capillary pressure decreases [124, 128]. Table 37.3 displays the hemodynamic changes and interventions of the long-term MCS devices.

VADs: weaning from VAD to recovery

Unloading the LV with a VAD leads to reverse remodeling of the heart. Some patients will normalize the cytoskeleton integrity by decreasing neurohumoral and cytokine activation. The reverse remodeling process has been described in patients with DCM. During the VAD support, optimization of heart failure medical treatment takes place with angiotensin-converting enzyme inhibitors (ACE-Is), β-blockers (preferably carvedilol), and aldosterone antagonists. Also, patients should undergo extensive physical therapy and nutritional support to maintain and improve their strength. The criteria used for myocardial recovery and candidacy for LVAD explantation are sinus rhythm, trivial mitral regurgitation, LV ejection fraction ≥45%, and LV end-diastolic diameter ≤ one standard deviation below mean for age (≤55 mm for adult-sized patients) along with serum brain natriuretic peptide (BNP) < 100 pg/mL. In a report, including pediatric and adult patients with DCM, 8.8% of patients weaned to recovery. In this study, patients were more likely to be weaned to recovery if they were younger and had a pulsatile VAD [129]. Several case reports or case series of children recovering from acute myocarditis after VAD support have been published [130]. Younger patients (<2 years) and with myocarditis have the highest chance of recovery.

Anesthesia, analgesia, and sedation for mechanical support

Patients who require ECMO or VAD support due to failure to wean from CPB have been under general anesthesia for the surgical procedure. The sedation should continue during the insertion of the long-term MCS system. In addition, plans should continue for sedation and analgesia to smooth the transition of care in the ICU. Patients requiring ECMO in the ICU are already intubated, have invasive pressure monitoring, and receive infusions for sedation and analgesia. If a patient needs the airway secured before initiation of ECMO, the surgical team should be immediately available in preparation for circulatory collapse after the induction of anesthesia. There are specific pharmacological considerations when anesthetizing children receiving mechanical support of the circulation.

Drug disposition changes on mechanical support

Critically ill patients have poorly predictable drug pharmacokinetics secondary to altered hepatorenal perfusion and function, drug interactions, reduced protein binding, and renal replacement therapy. The patient on ECMO will have additional pharmacokinetic changes related to the volume of the circuit, the polymer components, and the altered perfusion and drug elimination. On initiation of ECMO, the fluid in the membrane oxygenator and tubing adds 200–300 mL to the circulating volume, depending on the circuit. This effect is relatively insignificant for drugs with a high volume of distribution (V_d), such as fentanyl, which shows relatively little change in plasma concentration, following ECMO initiation, drugs will diffuse back into the plasma from the tissues.

Pharmacokinetics alteration on ECMO is common and affects about 70% of the drugs used in children [131]. Drugs with lower V_d, (e.g., gentamicin, vancomycin, and nondepolarizing neuromuscular blockers) have a larger dilutional effect. Therefore, a higher loading dose is needed, but the dosing interval should be the usual [132, 133]. The hemodilution of ECMO also associates with a reduction in plasma protein concentration, increasing the free fraction of highly protein-bound drugs (e.g., teicoplanin or ceftriaxone). The increased free fraction of the drug will cause a transient increase in clinical effect, but there will also be an increase in

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drug diffusion to the tissues and, hence, a reduction in plasma concentration. The addition of albumin to the pump circuit will reduce this effect.

Another pharmacokinetic ECMO effect is the absorption by the circuit. Absorption can occur on the large surface area of tubing or the membrane oxygenator of the ECMO circuit, further increasing the V_d. Conversely, sequestered drugs are released back into the circulation, which adds further unpredictability of drug disposition and may prolong the drug's effect [134]. The degree of sequestration depends on the materials used in the ECLS circuit and the nature of the drug. ECLS PVC tubing and the membranes may comprise several biomaterials, including silicone rubber, polypropylene, PMP, or PVC [135]. In general, drugs are more likely to adhere to the PVC if they are highly lipophilic, such as opioids, propofol, and benzodiazepines. *in vitro* studies show that morphine has more negligible adsorption from PVC than fentanyl, 40% for morphine vs. 86% for fentanyl [136]. Most of this adsorption is onto the tubing itself rather than the membrane oxygenators, although newer modified surface-coated PVC tubing still sequesters approximately 40% of fentanyl and 35–58% of morphine [136].

Multiple factors in a heterogeneous patient population make an accurate prediction of drug doses extremely difficult. Nevertheless, appreciation of the issues helps the clinician to make sensible drug management decisions, particularly when initiating ECLS and changing the circuit. Appropriate sedative and analgesic dosing can be difficult, running the risks associated with under-and over-sedation. Under-sedation is associated with pain, ventilator desynchrony, and inadvertent line removal. Alternatively, oversedation is associated with prolonged ventilation and hospital-acquired infections. Vigilant clinical monitoring is therefore mandatory. Prolonged analgesic infusions with fentanyl and morphine are associated with tolerance; however, the long duration of action makes morphine the preferred analgesic. Careful drug monitoring should always be employed where possible (e.g., gentamicin) to guide dosing regimens.

KEY POINTS: ANESTHESIA AND ANALGESIA FOR MECHANICAL SUPPORT

- Pharmacokinetics of medications can be significantly altered by ECMO or VAD.
- V_d is increased, and drugs with low V_d, such as nondepolarizing neuromuscular blockers, will have a lower concentration and require a higher loading dose.
- Hemodilution may reduce plasma proteins, which would increase the free fraction of highly protein-bound drugs.
- Lipophilic medications, such as opioids, benzodiazepines, and propofol will bind to the circuit with the following consequences:
  - Lower plasma levels are seen when initiating the medication.
  - There may be continued release of the medication from the circuit after the drug is discontinued.

Anesthesia, analgesia, and sedation for mechanical support patients undergoing NonCardiac surgery

Technological improvements have allowed MCS to expand to the pediatric population. However, because heart transplantation continues to be limited by organ availability, the number of patients having MCS as DT continues to increase, representing 73% in the Intermacs 2020 Annual Report [137, 138]. This has, in turn, increased the incidence of these patients presenting for noncardiac procedures, currently being between 20 and 50% [139]. For this reason, it is imperative to have a comprehensive understanding of the device characteristics and the perioperative anesthetic implications.

Preoperative management

Preoperatively, it is important to know the type of MCS device, its baseline parameters, and any additional inotropic support. Besides the formal review of systems, coagulation status is usually affected by anticoagulation and antiplatelet aggregation agents. Although there is a lack of standardized guidelines, each MCS device will have goal international normalized ratio (INR) manufacturer recommendations. The perioperative bridging strategy will also institution dependent. Ultimately, the anticoagulation strategy is tailored to the patient's history, surgery type, and urgency [140]. Additionally, it is crucial to consider these patients may have some degree of liver dysfunction resulting in factor deficiency. Acquired von Willebrand disease (vWD) type 2A in the setting of a high-shear continuous-flow VADs may also generate platelet dysfunction [141]. It is of paramount importance to assess the RV function to determine the LV/MCS preload. These patients are commonly on ACE-Is, angiotensin-receptor blockers (ARBs), beta-blockers, and nitrates, all of which may have significant effects on intraoperative hemodynamic management. Because of the high incidence of cardiac arrhythmias in these population, it is frequent to have implantable cardioverter defibrillators (ICDs) [134]. Consequently, it is essential to address the presence of such devices, their characteristics, the patient's dependency on them, and the need for interrogation and deactivation before the procedure. Noncardiac procedures in this patient population should be performed in a tertiary center. A multidisciplinary team is needed, including VAD coordinators, cardiologists, cardiothoracic surgeons, anesthesiologists, and intensivists. Recent studies comparing noncardiac vs. cardiac fellowship-trained anesthesiologists have shown similar techniques and outcomes during low-risk noncardiac procedures and surgeries [135].

Intraoperative management

It is essential to connect the MCS to a power source. Backup batteries, inotropes, vasopressors, and inhaled NO may be required. Regarding intraoperative monitoring, the pulsatility index may vary when managing patients on VADs, depending on the speed, afterload, and native LV contractility. Therefore, essential monitors, such as the pulse oximeter and noninvasive blood pressure (NIBP) cuff may be unreliable [136]. In this sense, near-infrared spectroscopy (NIRS) will aid in assessing regional oxygenation, while using an NIBP

cuff with a Doppler or an arterial catheter will help obtain accurate blood pressure measurements [142]. A central venous catheter or TEE may help assess RV function and volume status. The surgical approach may have significant hemodynamic effects. Thoracic or abdominal procedures requiring cavitary insufflation or extreme positioning (e.g. reverse Trendelenburg) decrease the preload, increase the afterload, and increase the $PaCO_2$, negatively affecting the VAD hemodynamics [143]. Finally, appropriate adjustment of mechanical ventilation, preventing arrhythmias, and volume-overload in nonvolume responsive states is of paramount importance [144].

Postoperative management

Patients with MCS devices recovering from noncardiac surgery need to be in a unit with personnel familiar with their management. It is essential to prevent hypoxia and hypercarbia during anesthesia recovery, increasing PVR and worsening VAD function. Moreover, bucking and vomiting should also be avoided, increasing intrathoracic pressure and RV afterload. Consequently, postoperative nausea and vomiting (PONV) prophylaxis are mandatory. Resuming anticoagulation should be discussed with the surgical and cardiology team. The AICD needs to be restored to its baseline settings. Recently, the AHA published guidelines for CPR in patients with VAD [145]. The challenge in this population is to promptly diagnose circulatory arrest in a clinical setting which is misleading due to VAD physiology. The first step is to assess perfusion. Patients lacking perfusion suggest primary device failure (e.g., disconnection, driveline breakage, or driver failure). First, rule out nonVAD causes of arrest. Bedside point of care echocardiography helps to identify reversible arrest causes. If the VAD is nonfunctioning, it should be restarted after inspection of the power source and driveline. If the circulatory failure is not attributable to VAD failure, the guideline recommends CPR with chest compressions. The only exception is with STAH patients in which CPR and inotropes are detrimental.

Anticoagulation, antifibrinolytics, and platelet antiaggregation therapies

Blood exposure to the ECMO circuit causes cellular activation of complement, coagulation, fibrinolysis, and inflammation. These effects are more pronounced in neonates and infants because of their lower blood volume than the circuit size [146]. Anticoagulation is mandatory when initiating ECMO. Thus, the challenge is to achieve adequate anticoagulation without producing hemorrhagic complications. Unfractionated heparin (UFH) is the first-line drug to achieve anticoagulation on ECMO. Before ECMO cannulation, a bolus of UFH of 100 units/kg is administered to achieve an activated clotting time (ACT) of more than 180–200 seconds. ACT is a real-time bedside test that measures whole blood clotting (platelets, red cells, and clotting factors) after exposing the blood to activators (kaolin or celite). The ACT does not correlate well with activated partial thromboplastin time (aPTT) or antifactor Xa in heparinized neonates receiving. [197] Postcannulation UFH drip is started with the aim of keeping the ACT between 180 and 220 seconds followed by an infusion of 8 units/kg/hour (range 6–60 units/kg/hour) and adding heparin to the pump prime. Neonates have higher heparin needs secondary to faster heparin clearance and volume of distribution (higher water content). During ECMO, the primary source of heparin clearance is inactivation in the circuit. Therefore, we transfuse platelets to keep platelet count >100,000/mm^3 and cryoprecipitate to keep fibrinogen over 150 mg/dL. In patients with heparin-induced thrombocytopenia, direct thrombin inhibitors have been used in pediatric ECMO [147]. The selected use of factor VII helps in refractory bleeding on ECMO, but it has also been associated with life-threatening thrombosis [148]. The ATIII levels should be checked and kept above 70% to avoid thrombotic complications.

Point of care testing is use in ECMO and VAD placement. The most important parameter to follow is maximal graph amplitude (MA in TEG®) or maximum clot firmness (MCF in ROTEM®). It is measured in millimeter and reports the maximal clot firmness through the increase in fibrin polymerization, platelets and FXIII. The use of FIBTEM or functional fibrinogen can differentiate between the platelets or fibrinogen contribution to the clot firmness. It is our practice to send a two channel ROTEM (HEPTEM with heparinase and FIBTEM) upon rewarming of CPB [149] (see Table 37.4).

Our philosophy is that anticoagulant agent(s) should start once the coagulation profile is normal postVAD insertion. In most of the cases, patients are in a "hypocoagulable" state early after surgery (<48 hours postoperative). The etiology of bleeding includes low platelet counts, platelet dysfunction, or inadequate coagulation factors, such as fibrinogen. Therefore, initiation of anticoagulation occurs typically 24–48 hours postoperatively. Currently, most of the institutions follow the Edmonton antithrombotic protocol once the patient is discharged from the ICU. This protocol involves a three-drug regimen: antiplatelet agent (e.g., aspirin clopidogrel, or dipyridamole), and either warfarin (≥12 months)

Table 37.4 ROTEM normal values

	CT (sg)	α-angle (°)	CFT (sg)	A10 (mm)	MCF (mm)	LI30 (%)	ML (%)
INTEM	100–240	70–83	30–110	44–66	50–72	94–100	0–15
EXTEM	38–79	63–83	34–160	43–65	50–72	94–100	0–15
FIBTEM	n.d.	n.d.	n.d.	7–23	9–25	n.d.	n.d.
HEPTEM	100–240	70–83	30–110	44–66	50–72	94–100	0–15
APTEM	38–79	63–83	34–160	43–65	50–72	94–100	0–15

Abbreviations: A10, amplitude 10 minutes after CT; CFT, clot formation time; CT, clotting time; LI30, lysis index 30 min after CT; MCF, maximun clot firmness; ML, maximum lysis; mm: millimeters; n.d.: no data; sg: seconds.

or enoxaparin (<12 months) [148]. Platelet aggregation studies are used to follow the platelet function and guide the administration of aspirin and dipyridamole. Infection will increase the risk of clotting, and anticoagulation monitoring should increase in frequency when infection is suspected.

Anti-infective therapy

Bleeding and infections continue to be the leading cause of adverse events in patients with VADs [137]. The incidence of MCS infections varies between 13 and 80%, depending on the definition [150]. Bacteria represent the primary etiology of early and late infections, with fungi representing <10% of the time. *Staphylococcus aureus* and *Staphylococcus epidermidis* cause more than 50% of the infections. The most common gram-negative bacteria is *Pseudomonas aeruginosa* (22–28%). Candidemia (caused by *Candida albicans* in 70% of the cases) is the most common fungal infection (1.3–9.7% of cases), with a 15–25% mortality rate [151]. The most common risk factors for infection in MCS are pulsatile devices, older age, comorbidities, intravascular lines, open sternum, prolonged ICU stay and duration of MCS support. There are currently no randomized controlled trials studying the optimal perioperative antimicrobial prophylaxis regimen for MCS implantation. However, the International Society for Heart and Lung Transplant (ISHLT) MCS consensus expert panel recommends always targeting *Staphylococcus* species and, in colonized patients or centers with high methicillin-resistant *S. aureus* (MRSA) prevalence, coverage for MRSA. The duration of the antimicrobial prophylaxis should not exceed 48 hours after the procedure. Routine broad-spectrum gram-negative prophylaxis and antifungal prophylaxis are not required unless guided by local institutional epidemiology data. In case of MCS infections, it is based on identification of the specific pathogens, infection location site (pump, cannula, pocket or drive-line), infection type (infective endocarditis, bloodstream infection, and mediastinitis) and transplant candidacy status (BTT vs. DT). Frequently, surgical debridement, collection drainage, device exchange, or even urgent heart transplant may be necessary. Patients with severe MCS-related infection or sepsis may have increased short-term mortality rates and are ineligible for transplantation [152].

Outcomes and complications of extracorporeal support

The number of all age-group cases requiring ECMO and the number of reporting centers have been increasing significantly over the past 15 years [37]. The outcome depends on the age, deployment timing, comorbidity, indication for support, and severity of illness. In children, results of ECMO for CHD are generally worse than for respiratory disease. However, it must be remembered that although the overall rate of ECMO in congenital heart surgery centers has remained constant at 2–3%. But the demographic of children requiring ECLS has changed in recent years, including more complex patients. Children undergoing ECPR, transplants, and complex congenital heart surgery (e.g., stage 1 hypoplastic left heart) are represented in the figures with increased frequency [36]. The ECMO survival to hospital discharge in children with heart disease is 40–45%, which is lower than the survival rate in children with respiratory disease. However, most outcome data are based on the ELSO registry, which has collected over 50,000 patients since 1984. Unfortunately, cardiorespiratory function, neurodevelopmental outcomes, and quality of life are not collected by ELSO [36]. In addition, until 2013, there was no severity of illness scoring within the registry, so that, specific data have so far been difficult to interpret; for example, VA-ECMO for neonates with respiratory failure has a mortality of 29%, but with VV-ECMO, the mortality is 16%. Without knowing the illness severity, we cannot ascertain what impact the mode of ECLS has on these figures.

Critically ill patients requiring central or peripheral mechanical support are at risk of serious complications, most of them related to organ hypoperfusion, bleeding, coagulopathy, systemic inflammatory response, embolic events (air or thrombus), hemolysis, and sepsis. In addition, the design of the mechanical support carries an inherent risk. Oxygenators run the risk of red cell damage, and the tubing and multiple connectors risk clot formation and gas embolization. The frequencies of mechanical and patient-related complications are summarized in Tables 37.5 and 37.6. We see that overall mechanical failure is relatively uncommon but is associated with significant mortality. Of the patient-related complications, bleeding from the cannula and surgical sites remains a considerable risk that carries a high mortality. Unfortunately, there is a lack of data on the long-term consequences of ICH.

ECMO for cardiac support

Cardiac failure and sequelae of low cardiac output are the most common causes of mortality after ECMO for cardiac reasons [15, 36, 37]. For postcardiotomy patients, outcomes vary due to specific indication and deployment techniques. In these patients, if an arterial pulsatile waveform does not return after 72 hours of ECMO or VAD support, the prognosis is dismal, and transplantation or withdrawal is considered. Other prognostic indicators for ECMO, but not VAD, include urine output, renal function, and pH at 24 hours.

Overall, the rate of survival of ECMO in neonatal patients with cardiac disease is 42%, with pediatric survival of 51% [33]. Neonates following cardiac surgery for stage 1 palliation for HLHS represent the most common subgroup; 17% of patients require ECMO. Unfortunately, this group has a high early mortality of 57% [126]. Pediatric patients in all age groups with acute fulminant myocarditis requiring ECMO have a better prognosis than postcardiotomy patients; 60–80% survive to discharge [153]. The natural history for myocardial recovery is different in this group, and recovery can take days up to years. However, according to the ELSO registry, this survival figure is worse in neonates with enteroviral myocarditis at 33% [154].

These patients should transition to VAD from ECMO if there are no signs of recovery after 2 weeks [155]. There is a 57–61% survival rate and new VAD technology appears to reduce transplant waiting list mortality compared with long-term ECMO support [57].

Postcardiac transplantation ECMO requires ECLS commonly (14–17%). Acute graft dysfunction is the most common

Table 37.5 Mechanical complications of extracorporeal life support

Complication	Age group	Cohort	Number of cases (%)	Survival (%)
Oxygenator failure	Neonatal	Respiratory	1,529 (6)	53
		Cardiac	368 (7.6)	24
	Pediatric	Respiratory	681 (12.9)	43
		Cardiac	509 (8.8)	35
Tubing rupture	Neonatal	Respiratory	238 (0.9)	66
		Cardiac	42 (0.8)	24
	Pediatric	Respiratory	161 (3)	47
		Cardiac	94 (1.6)	37
Pump malfunction	Neonatal	Respiratory	439 (1.7)	66
		Cardiac	80 (1.6)	28
	Pediatric	Respiratory	132 (2.5)	47
		Cardiac	127 (2.1)	42
Cannula problems	Neonatal	Respiratory	2,978 (11.6)	67
		Cardiac	300 (6.2)	34
	Pediatric	Respiratory	814 (15.4)	51
		Cardiac	350 (6)	41

Source: Data from Thiagarajan et al. [37].
Mechanical related complications of extracorporeal life support (ECLS) divided into age group and cohort. Pediatric refers to age range 1 month to 16 years. Respiratory cohort refers to those with a respiratory indication for ECLS. Cardiac cohort refers to those with a cardiovascular indication for ECLS. Tubing rupture combines raceway rupture with other tubing rupture.

Table 37.6 Patient-related complications of extracorporeal life support

Complication	Age group	Cohort	Number of cases (%)	Survival (%)
Cannula site bleeding	Neonatal	Respiratory	1,845 (7.2)	64
		Cardiac	513 (10.5)	29
	Pediatric	Respiratory	870 (16.4)	51
		Cardiac	830 (14.3)	46
Surgical site bleeding	Neonatal	Respiratory	1,605 (6.3)	44
		Cardiac	1,540 (31.6)	30
	Pediatric	Respiratory	756 (14.3)	46
		Cardiac	1,836 (31.7)	42
Cardiac tamponade (blood/serous/air)	Neonatal	Respiratory	201 (0.7)	40
		Cardiac	317 (6.5)	29
	Pediatric	Respiratory	141 (2.6)	36
		Cardiac	327 (5.6)	43
Seizures (determined clinically)	Neonatal	Respiratory	2411 (9.4)	61
		Cardiac	363 (7.5)	29
	Pediatric	Respiratory	311 (5.9)	34
		Cardiac	419 (7.2)	24
Intracranial hemorrhage	Neonatal	Respiratory	1785 (7)	44
		Cardiac	548 (11.3)	23
	Pediatric	Respiratory	316 (6)	22
		Cardiac	277 (4.7)	26

Source: Data from Thiagarajan et al. [37].
Patient-related complications of extracorporeal life support (ECLS) divided into age group and cohort. Pediatric refers to the age range 1 month to 16 years. Respiratory cohort refers to those with a respiratory indication for ECLS. Cardiac cohort refers to those with a cardiovascular indication for ECLS.

reason for early survival is approximately 60% since the natural history is for many grafts to recover [36]. Long-term mortality after hospital discharge in children with cardiac disease is becoming appreciated; a recent study suggests 6% late mortality, often related to the severity of the cardiac condition or comorbidity; this was like the findings of a 5-year follow-up study from Canada [156, 157].

ECMO for respiratory support

The introduction of ECMO programs for neonates with respiratory failure produced significant improvement in outcome, 82% survival vs. 72% for historical controls [158]. Of the 51,000 patients requiring ECMO recorded to the ELSO Registry through 2016, 50% were for neonatal respiratory support, with 74% survival to discharge in this population

[33]. As always, however, the specific indication for ECMO impacts survival rates; neonates with CDH requiring ECMO have a 51% survival, whereas those with MAS requiring ECMO have an overall 94% survival [33]. Survival depends on preECLS factors (e.g., primary diagnosis, age, hypoxemia, acidosis), ECLS factors (e.g. cannulae, complications, duration), and postECLS status. Late mortality is primarily related to comorbidities [159].

The most common indication for ECMO for respiratory disease outside the neonatal period is viral pneumonia (20%) [37]. Overall pediatric hospital survival is approximately 57%. However, outcomes depend on both diagnosis (e.g., 83% survival for asthma, 23% for fungal pneumonia) and comorbidity (e.g. 59% for chronic lung disease, 5% for hematopoietic stem cell transplant) [160]. Survival declines with increasing time on mechanical support. In a study of 3213 children supported on ECMO, those requiring <14 days of support had 61% survival compared with 38% in those supported for more than 21 days. Male gender increased inotrope infusion and acidosis were independently associated with increased odds of death [161]. Age >10 years is associated with lower survival (50%) compared with infants and toddlers (57, 61%) [162]. Overall survival rates appear to have shown only small improvements over the last 10 years. However, the increased frequency of children with significant comorbidity offered ECMO is likely to have reduced the improvement in survival [163]. Despite improvement in ventilatory strategies, preECMO ventilation time of >2 weeks has worse hospital survival [164].

ECMO complicated by sepsis

Sepsis is a critical complication of ECMO, and its presence is a poor prognostic marker and increases the overall mortality [165]. Potential sources of sepsis include ventilator-associated pneumonia (VAP), bloodstream or cannula infections, mediastinitis, infections related to urinary catheters or other invasive lines, infected pressure sores, and *Clostridioides difficile* diarrhea [159, 165]. Mechanical support involves long-term invasive cannulas and access ports for sampling in critically ill patients who may be immunosuppressed, placing patients at significant risk of infection. Examination of the ELSO registry from 1998 to 2008 found that infections occurred in 11.7% of patients on ECMO. For adult, pediatric, and neonatal groups, the rates were 30.6, 20.8, and 10.1 infections per 1,000 ECMO days. Neonates and children have infections complicating their ECMO in 5.8 and 16.8%, respectively [33]. VA-ECMO was associated with the highest rate of infection in each group. As expected, the prevalence of infectious disease increases with time on mechanical support: 6.1% infection rate for <7 days ECMO, 30.3% in those requiring ECMO for >14 days [166].

The most common organisms were coagulase-negative staphylococci in the neonatal group (15.9% of all patients) and *Candida* in the older pediatric and adult groups (12.7% of all patients). *P. aeruginosa* was grown in 10.5% and *S. aureus* in 9.4%. Overall, those with culture-positive infections on ECMO had longer ECMO runs and a higher rate of death (57.6% infected vs. 41.5% noninfected). Even though fungal infections during extracorporeal support increase mortality, the presence of a fungal infection before ECMO does not contraindicate support [167]. Similar strategies may reduce these infections to those for central line infections and VAP [166].

ECMO and renal function

Renal function in the context of ECMO or CPB may be adversely affected due to hemodynamic impairment, ischemia–reperfusion injury, inflammation, and oxidative stress. Definitions of acute kidney injury (AKI) vary, and the ELSO registry data collection uses a high threshold of serum creatinine for their criteria (>1.5 mg/dL) [168]. With this definition, younger patients may be missed, and single-center reports of AKI differ from the ELSO registry data. Data extracted from ELSO for neonates and older children are presented in Table 37.7. These results reported in 2012 were like

Table 37.7 Renal injury during extracorporeal life support

Age group	Indication for support	Degree of acute kidney injury (AKI)	Number reported with AKI (% of total)	Survival number (% of total)	Cohort survival to discharge or transfer (%)
Neonatal	Respiratory	$[Cr]_{serum}$ 1.5–3 mg/dL	1,782 (7)	914 (51)	75
		$[Cr]_{serum}$ >3 mg/dL	345 (1.3)	126 (37)	
		Renal support required	5,067 (20)	2552 (50.3)	
	Cardiac	$[Cr]_{serum}$ 1.5–3 mg/dL	617 (12.7)	138 (22)	39
		$[Cr]_{serum}$ >3 mg/dL	92 (1.9)	24 (26)	
		Renal support required	2,038 (42)	476 (23.3)	
Pediatric	Respiratory	$[Cr]_{serum}$ 1.5–3 mg/dL	521 (9.9)	162 (31)	56
		$[Cr]_{serum}$ 1.5–3 mg/dL	242 (4.6)	69 (29)	
		Renal support required	2297 (43.6)	909 (39.5)	
	Cardiac	$[Cr]_{serum}$ 1.5–3 mg/dL	684 (11.8)	195 (28.5)	48
		$[Cr]_{serum}$ >3 mg/dL	261 (4.5)	79 (30)	
		Renal support required	2,215 (38.3)	761 (34.3)	

Source: Data from Thiagarajan et al. [37].

The association of AKI with extracorporeal life support (ELSO) stratified according to neonates <30 days old and pediatrics (1 month to 16 years). Renal replacement therapy refers to those requiring dialysis, hemofiltration or continuous arteriovenous hemodialysis.

a recent systematic review and meta-analysis of kidney injury on ECMO in children, whereby the overall incidence of AKI was 61.9, and 40.9% required renal replacement therapy. The increased hospital mortality related to AKI and AKI requiring renal replacement therapy showed an odds ratio of 1.7 and 3.64, respectively. Note that the incidence of AKI in the cardiac ECMO groups is higher than those in the respiratory groups. In a neonatal single-center study, NO ventilation and younger age at ECMO cannulation predictors acute kidney injury [169]. In this study, 64% had acute kidney injury, 30% classified as "risk," 23% as injury, and 11% as failure [170]. In addition to mortality, neonates with acute kidney injury associated with ECLS treatment are risk factors for developing chronic kidney disease. For example, in one study of neonatal ECLS survivors, 32% had signs suggestive of chronic kidney disease at median 8.2 years of follow-up, as defined by proteinuria, hypertension, or reduced glomerular filtration rate (GFR). The presence of AKI was the predictor, although maybe of minimal clinical significance [170].

Overall long-term survival

It would be shortsighted to restrict our focus on hospital discharge, as the combination of mechanical support and underlying disease will have a longer-lasting effect on the child's health [171]. Data are starting to reveal that the incidence of late death is significant. In a study of 741 children requiring ECMO, 469 survived the past 90 days. Of these survivors, 46 (10%) subsequently died. Of the children alive at 90 days, the highest survival was for MAS (97.9%), and the lowest survival was for CDH (73.6%). Congenital and acquired heart disease also carried a significantly increased risk of late death compared with MAS. The most common cause of late death was a cardiac failure in these cardiac patients, although some deaths were due to neurological injury, respiratory and renal failure. Other reports show consistent results; in a single-center study of children receiving ECMO for respiratory failure from 1987 to 2013, those who survived 90 days had a 93% survival in neonates and 89% in the pediatric population; the highest survival groups were due to meconium aspiration, trauma, and infectious disease. Patients who received VV-ECMO had significantly higher 10-year survival compared with VA-ECMO. This observation is probably related to the increased risk of complications with VA-ECMO, such as systemic ventricular wall tension and thrombosis, as well as the underlying conditions requiring VA-ECMO compared with VV-ECMO [172]. The late deaths were primarily related to underlying disease. This study did not focus on functional outcomes and quality of life. For children receiving ECMO for cardiac disease, the long-term outcome is worse. For example, a single-center long-term follow-up study showed despite 43% survival to hospital discharge, only 33% of patients were alive at median 6-year follow-up.

ECLS for CHD had an estimated five-year survival after ECMO of 32.3%. Surprisingly, some late deaths were in children with an underlying diagnosis of myocarditis who had been successfully weaned from ECMO after the acute illness [173]. As expected, in those who required ECLS for respiratory disease, the causes of late deaths were primarily due to respiratory failure or PHTN. Many of the other deaths were due to complications of prematurity [173]. Therefore, we can conclude that for cardiac and respiratory indications for ECMO, almost all the late deaths were related to the primary underlying disease rather than complications of the mechanical support itself.

Neurological outcome

Brain injury is common in children receiving mechanical support. A nationwide study in the Netherlands reviewed ultrasound images over 20 years on all neonates (>2 kg and >34 weeks' gestation) who received ECMO. The overall incidence of injury was 17.3%, of which 8.8% had a primary hemorrhage. Stroke occurred in 5% and lobar hematoma in 2.2%. Survival of patients without brain injury was 75.5% compared with 54.7%, and the incidence of brain injury in preterm neonates was 31.5% compared with those born at term (14.5%). As expected, three-quarters of the premature brain injury was primary hemorrhage. Notably, the prevalence of brain injury did not differ over the 20 years, despite alterations in the technical management of the ECMO circuit [174]. Much of the longer-term neurological outcome data available involves neonatal follow-up – particularly for respiratory disease. Overall, 5–10% of neonates who survive ECMO for respiratory illness have severe neurological impairment. The remaining survivors are at risk of more subtle neurodevelopmental problems. Long-term follow-up has demonstrated intelligence is generally comparable to previously healthy children [175]. However, a relatively high number of ECMO survivors attended special education compared with the general population. Neuropsychological testing has shown despite a comparable IQ, a large group of previous ECMO patients exhibits selective attention deficits, working memory impairment, reduced operating speed, and the need for extra help at school [175–177]. Children on ECMO for CDH had lower IQ and worse neuropsychological outcomes than other respiratory diagnoses [176]. Motor function development is generally favorable in neonatal ECMO. Survivors measured in the preschool phase of growth. However, more complex task deficits become apparent at an older age. For example, at 1 year of age, normal motor function is identified as standard in 84%, whereas only 43% are average at 7 years of age [178]. Seizures are common in children treated with ECMO, and recent evidence suggests that we may be underestimating the true incidence. In one small study of 19 non-neonatal pediatric patients, four children had seizure activity, of which three were nonconvulsive. Although the seizures were not associated with mortality, the abnormal EEG activity often occurred without associated clinical findings. This seizure activity may indicate CNS injury although the neurological outcome in this population was unknown. However, it is known that neonates treated with ECMO who had seizures have a higher risk of developmental delay. A single-center 6-year follow-up of ECMO for cardiac disease showed high morbidity, including over 50% had seen a neurologist and nearly 20% having ongoing neurology follow-up. Nearly, 50% of survivors had some degree of learning disability, although the time-course and the exact nature of these disabilities are unclear [172]. Approximately, one-third of survivors needed ongoing physiotherapy, occupational therapy, or speech pathology.

The recommendations for long-term neurodevelopmental follow-up depend on neurological comorbidity, the nature

and extent of the underlying disease, and ECMO indication [179]. Sensorineural hearing loss has been reported in patients after ECMO. Risk factors include prolonged ECMO, ICH, sepsis, and seizures. In 136 neonatal ECMO survivors followed up to 5–12 years of age, the incidence of bilateral sensorineural hearing loss >20 dB was 3.7%; however, median intelligence and language development were normal. Risk factors were related to the premorbid condition and other therapies, such as aminoglycosides rather than the ECLS treatment [180].

Quality of life

Neurological injury is common during ECMO, as is long-term cardiac and respiratory dysfunction. Despite the inherent difficulties in defining quality of life, assessment tools are becoming available to measure quality of life in children, including disease, psychosocial impact, and dynamic environment [181]. Limitations of acquiring meaningful data still exist, however, such as difficulty in assessing children's quality of life under 8 years of age and delineating the effects of ECMO from those of the underlying disease. In addition, there are the practical difficulties of interpreting data where there is invariably a low proportion available for study at long-term follow-up (<50%). Most studies studying the quality-of-life measurements have occurred in children receiving ECMO for cardiac disease and are single-center studies.

With these caveats in mind, results have been variable. Follow-up of patients receiving ECMO for cardiac disease in one 4-year follow-up study demonstrated mean pediatric quality of life summary scores were significantly lower than nonECMO children with chronic health conditions and CHD [182]. Another study examining those who received mechanical support as a bridge to transplant showed physical and psychosocial scores to be equivalent [183]. Recently, a longer-term (11–24 years) follow-up study of 20 neonates and children receiving ECMO used a self-reporting pediatric quality of life questionnaire. Ninety percent had no disability with complete standard quality of life, and 95% had no cognitive impairment [184].

In neonates receiving ECMO for primarily respiratory disease, one study concluded that they had a significantly worse quality of life at 5 years of age than a reference group based on maternally reported health-related quality of life scores. Delayed neuromotor development, cognitive and behavior problems, and a disabled maximum exercise capacity affected the outcome [185]. Another study looking at pediatric cardiac ECMO survivors also found their maternal reported health-related quality of life to be lower than that of the controls but like children with complex cardiac disease. In contrast, the psychosocial quality of life was like the general population. Interestingly, the children old enough to report on their questionnaire suggest their quality of life is equal to or better than their peers [186]. It is consistent with a more recent study of 22 patients median 5 years of follow-up where parents reported reduced quality of life compared to healthy children. However, those over 12 years old able to self-assess showed scores comparable with healthy controls [187]. Overall, regardless of the range of psychosocial and physical disabilities, long-term survivors of CHD requiring ECMO report their quality of life to be quite good [188].

Comparing outcomes and complications of VAD and ECMO

Given their differing roles, timing, indications, and practicalities, it is not always possible to directly compare outcomes after ECMO with VAD. ECMO is more familiar and more commonly used in children because VAD cannot provide respiratory support or be used for PHTN. VAD advantages include lower prime volume, less hemolysis, reduced anticoagulation requirement, and fewer bleeding complications. The VAD circuit has fewer access ports, which reduces the chance of infection, and the patient can ambulate and go home. In addition, the time-dependent increase in complications seen with ECMO does not seem to be as evident with VAD [57]. Long-term support with VAD is therefore associated with fewer ECLS-related complications while bridging to recovery or transplant. In a larger, less selective multicenter trial, children supported for 1–435 days showed a 12-month survival of 75%, which comprised 64% successfully transplanted, 6% recovered and explanted, and 5% with device in situ at 12 months. The most common cause of death on EXCOR was a respiratory failure (50% of deaths), while 33% were due to neurological injury, with thromboembolic strokes being more common than hemorrhagic strokes. Smaller patient size (and age) was also associated with early mortality. Mortality appeared to reduce in centers with higher implantations; however, this difference was not significant when adjusted for other baseline characteristics [189].

Although no extensive studies compare ECMO and VAD used as a bridge to transplantation, this study reveals improved survival for children >5 kg supported by EXCOR compared with outcomes of long-term ECMO. The survival for children <5 kg in the study was poor; 21 out of 33 died, so the advantage over ECMO seen in larger children has yet to be demonstrated in this group [189]. One center studied children requiring mechanical assistance for primary graft failure following heart transplantation and had 44 patients requiring continuous flow VAD or VA ECMO. VAD needed longer bypass time to insert and was associated with more bleeding complications requiring exploration ($p = 0.0047$), a higher incidence of renal replacement therapy ($p = 0.0045$), higher in-hospital mortality ($p = 0.16$), and higher 3-year mortality ($p = 0.13$) [190]. From the physiological point of view, a study in piglet models comparing ECMO with pulsatile and continuous-flow VADs showed an improved LV blood supply/demand ratio in both VAD and ECMO groups. In addition, LV filling pressures and LV workload were similarly reduced in the pulsatile VAD and ECMO groups. However, VAD demonstrated an improved global myocardial blood supply/demand ratio compared with ECMO [188]. It is not known whether these cardiovascular changes induced by VAD would lead to improved reversed ventricular remodeling of the myocardium.

Other outcome issues

Volume of cases

A retrospective study of 7,322 pediatric patients supported with ECMO found that after adjusting for case-mix, surgery complexity, and year of treatment, the low-volume centers (average <20 cases/year) had significantly higher odds of

death compared with the medium- and higher-volume centers. The minimum annual caseload associated with lower mortality was 22 [191]. It is consistent with more recent studies suggesting a similar pattern of lower mortality is true in both neonates and adults in those centers with a higher age-specific volume of cases [192]. Interestingly, the trend was not seen in this study in the pediatric population. However, a more recent survey of US pediatric centers found lower risk-adjusted mortality in those centers with more than 30 ECMO runs per year in all pediatric ages [193].

Parental outcomes

A study of the parents of children who were successfully bridged to recovery demonstrated that 20% suffered symptoms of post-traumatic stress disorder. This issue has potential implications for the information we deliver to parents. Therefore, screening and developing service interventions for parents suffering from these symptoms are advised [194].

KEY POINTS: COMPLICATIONS AND OUTCOMES OF MCS

- Survival after ECMO is significantly better when used for respiratory support than when used for cardiac support.
- Survival among patients requiring cardiac support is significantly better for cardiomyopathy than for post-cardiotomy patients.

The future

Tomorrow ECMO

Over the last few years, technology in the pediatric field has not progressed significantly; there is still no pediatric Cardiohelp™ (Maquet Cardiopulmonary AG, Hirrlingen, Germany), available even though is available for adults a decade ago. Companies are reticent to spend significant research and development on new products with limited demand or significant regulatory hurdles. Spectrum is evolving its Quantum platform so that the ECMO system can potentially integrate more effectively with the electrical medical record. The efficiency of devices will be incrementally improved, allowing for rapid, simple ECMO initiation; however, no significant technological leap is on the horizon. Improvement allowing stable long-term ECMO support will result from using a less traumatic cannula, such as Berlin Heart cannula & anticoagulation regimens that use a cocktail rather than relying on heparin alone. NO, prostacyclin and bivalirudin will be the vanguard of maintaining anticoagulation. Heparin niche will be as a "fine control" (e.g., < 10 units/kg/min). NO has many other benefits which should result in better organ perfusion during ECLS with less morbidity (e.g., improved neurological sequelae and kidney function). Donor blood has no nitrosothiol levels resulting in poor organ perfusion even in high PaO_2 and high hemoglobin resulting in organ ischemia. Future devices will have NO eluting surfaces or use systems whereby NO is generated from room air via a plasma arc (Beyond Air), enabling routine NO use without the high cost [94, 195].

Tomorrow VAD

The future of VAD in children will continue growing in the next few years. The reason for this growth is the expanding indications, improved safety profile, and technological improvement. In addition, the use of pediatric VAD as DT, such as muscular dystrophy and failing single ventricle [12]. Thus, prospects of pediatric VADs are undoubtedly encouraging due to technological adaptations, such as continuous flow device miniaturization [196]. Finally, the expanded VAD use in children will bridge the gap between a stable pool of heart transplant donors and an increasing end-stage heart failure pediatric population.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

4 Barbaro RP, Paden ML, Guner YS, et al. Pediatric extracorporeal life support organization registry international report 2016. ASAIO J 2017;63(4):456–63. This report is to describe the international growth, outcomes, complications, and technology used in pediatric extracorporeal life support (ECLS) from 2009 to 2015 as reported by participating centers in the Extracorporeal Life Support Organization (ELSO). Since 2009 21,907 received ECLS with an overall survival to hospital discharge rate of 61%.

23 del Nido PJ, Dalton HJ, Thomson AE et al. Extracorporeal Membrane Oxygenator rescue in children during cardiac arrest after cardiac surgery. Circulation 1992;86:II 300–4. This is the first article to demonstrate the benefit of ECMO as rescue for cardiac arrest, termed ECPR. Overall early survival was seven of 11 (64%), with one patient requiring heart transplantation due to irreversible cardiac dysfunction. One child died late (1 month) after ECMO support. There were no long-term sequelae in the survivors.

25 Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL, et al. Part 4: Pediatric basic and advanced life support 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 2021;147(Supplement 1):S88–159. The updated guideline addresses the use of Extracorporeal cardiopulmonary resuscitation in selected pediatric patients with cardiac disease in the intrahospital setting

28 Lasa JJ, Rogers RS, Localio R, et al. Extracorporeal cardiopulmonary resuscitation (E-CPR) during pediatric in-hospital cardiopulmonary arrest is associated with improved survival to discharge. Circulation 2016;133(2):165–76. The authors demonstrate that E-CPR in children with in-hospital CPR of ≥10 minutes duration was associated with improved hospital discharge survival and favorable neurological outcomes compared with C-CPR.

49 Davies AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Critical Care Med 2017 Jun;45(6):1061–93. The new recommendation consider de use of a "recognition bundle" for rapid identification of patients with septic shock, "resuscitation and stabilization bundle" to adherence to best practice, and a "performance bundle" to identify and overcome perceived barriers.

95 Tume SC, Conway J, Ryan KR, et al. Developments in pediatric ventricular assist device support. World J Pediatr Congenit Heart Surg 2019;10(6):759–68. The author presents a focused review of the inpatient critical care environment. They discuss the recent field

developments and focus on challenging patient populations, the emergence of temporary support, management of anticoagulation, and diagnostic approach to stroke in VAD support.

98 Morray BH, Dimas VV, McElhinney DB, et al. Patient size parameters to guide use of the Impella device in pediatric patients. Catheter Cardiovasc Interv 2019;94(4):61. The authors define anthropomorphic and anatomic measurements in a creative study to guide providers in patient selection for MCS using the Impella devices.

106 Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC, Colombo PC, et al. A fully magnetically levitated circulatory pump for advanced heart failure. N Engl J Med 2017;376(5):440–50. In this randomized study of patients with advanced heart failure, the authors compared either the new centrifugal continuous-flow pump or a commercially available axial continuous-flow pump. The fully magnetically levitated centrifugal-flow pump was associated with better outcomes at six months than was the implantation of an axial-flow pump, primarily because of the lower rate of reoperation for pump malfunction.

157 Iguchi A, Ridout DA, Galan S, et al. Long term survival outcomes and causes of late death in neonates, infants and children treated with extracorporeal life support. Pediatr Crit Care Med 2013;14:580–6. A total of 741 children with 272 early deaths (36.7%) and 46 late deaths (6.2%) were included. Median follow-up time in survivors was 7.1 (interquartile range, 3.0–11.9) years. There was increased risk of late death in congenital diaphragmatic hernia, CHD, and acquired heart disease ($P < 0.001$, $P < 0.01$, $P = 0.01$) in comparison with the risk in meconium aspiration syndrome.

174 Raets MMA, Dudink J, Ijsselstijn H, et al. Brain injury associated with neonatal extracorporeal membrane oxygenation in the Netherlands: a nationwide evaluation spanning two decades. Pediatr Crit Care Med 2013;14:884–92. Brain abnormalities were detected in 17.3%: primary hemorrhage was most frequent (8.8%). Stroke was identified in 5% of the total group, with a notable significant preference for the left hemisphere (in 70%). Lobar hematoma (prevalence 2.2%) was also significantly left predominant.

Appendix: Pediatric Cardiovascular Anesthesia Drug Sheet (September 2022)

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Drug doses and treatments are those commonly recommended; each patient's treatment must be individualized, drug doses double-checked for accuracy, and drug concentrations and modes of administration used according to local guidelines. The information here is current at the time of publication; however, the practitioner must always be aware of new recommendations and remains responsible for determining the best course of treatment. Consult the textbook, hospital formulary, or authoritative internet resources for a complete listing of indications, contraindications, interval dosing schedules, and side-effects of these drugs and treatments. All drugs are intravenous, unless otherwise noted. Drugs denoted with an asterisk (*) are not approved by the US Food and Drug Administration (FDA) as of May 2021. Many drugs are not specifically labeled for pediatric use by the US FDA; however, the physician may choose to administer these drugs for specific indications, if in their judgment the drug will be safe and effective. The source for dosing information is the Texas Children's Hospital formulary, current as of May 2021, except as otherwise noted in the references.

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AL Grawany

Vasoactive infusions		
Clevidipine [1]	0.5–7 μg/kg/min	Loading: 10–15 μg/kg
Dobutamine	2–20 μg/kg/min	
Dopamine	2–20 μg/kg/min	
Epinephrine	0.03–1 μg/kg/min	
Esmolol	200–1000 μg/kg/min	Loading: 100–500 μg/kg
Fenoldopam	0.1–0.8 μg/kg/min	
Isoproterenol	0.03–1 μg/kg/min	Maximum dose 2 μg/kg/min
Levosimendan [2]*	0.05–0.1 μg/kg/min	Loading: 6–12 μg/kg over 1 hour
Liothyronine (Triostat®,T_3) [3, 4]	0.05–0.15 μg/kg/hour	
Milrinone	0.25–0.75 μg/kg/min	Loading: 50 μg/kg over 10–60 minutes
Nesiritide	0.01 μg/kg/min; at intervals of 3 hours, dosage may be increased by 0.005 μg/kg/min to the maximum of 0.03 μg/kg/min	
Nicardipine	0.5–2 μg/kg/min	
Nitroglycerine	0.25–3 μg/kg/min	
Nitroprusside	0.3–3 μg/kg/min	
Norepinephrine	0.03–1 μg/kg/min	
Phenylephrine	0.05–0.5 μg/kg/min	
Prostaglandin E1	0.01–0.1 μg/kg/min	
Vasopressin	0.01–0.04 units/kg/hour	
Vasoactive bolus drugs		
Atropine	IV: 0.01–0.02 mg/kg IM: 0.02 mg/kg	
Calcium chloride	10 mg/kg IV	
Calcium gluconate	30 mg/kg IV	
Enalaprilat	5–10 μg/kg/dose IV Q8–24H; max. 5 mg/dose	
Ephedrine	0.1 mg/kg IV max. 5 mg	
Epinephrine	0.5–10 μg/kg IV	
Hydralazine	0.1–0.2 mg/kg IV	
Labetalol	0.2–1 mg/kg IV	
Methylene blue [5–7]	1–2 mg/kg IV	
Phenoxybenzamine	0.25–1 mg/kg IV	
Phentolamine	0.05–0.2 mg/kg IV	
Phenylephrine	0.5–3 μg/kg IV	
Antiarrhythmic agents		
Adenosine	First dose: 0.1 mg/kg IV (max 6 mg) Second dose: 0.2 mg/kg IV (max dose 12 mg)	
Amiodarone	10–15 mg/kg/day	Loading: 2.5–5 mg/kg or a maximum of 300 mg IV over 5–10 minutes. Additional boluses of 5 mg/kg or a maximum of 150 mg IV push may be given with a maximum total dose not to exceed 25 mg/kg or 2.2 g in 24 hours
Lidocaine	20–50 μg/kg/min	Loading: 1 mg/kg; repeat if the dose infusion is initiated more than 15 minutes after initial bolus
Procainamide	20–80 μg/kg/min (max 2 g/day)	Loading: 3–6 mg/kg/dose over 5 minutes, not to exceed 100 mg/dose; may repeat every 5–10 minutes to the maximum total loading dose of 15 mg/kg; do not exceed 500 mg in 30 minutes
Verapamil	0.1–0.3 mg/kg/dose (max. 5 mg) Repeat dose 30 minutes after the initial dose as needed (max second dose 10 mg)	

Pulmonary hypertension medications		
Inhaled nitric oxide	1–20 PPM	
Epoprostenol [8]	Intravenous: 1–2 ng/kg/min initial infusion; increase by 1–2 ng/kg/min every 4–8 hours to 25–40 ng/kg/min; must be given in dedicated intravenous line Inhaled: 20–50 ng?kg/min continuous infusion	
Iloprost [9]	Inhaled: Initial: 0.5 mcg/kg over 10 minutes Subsequent Dosing: 1–2 mcg/kg over 10 minutes	
Sildenafil [10, 11]	0.067 mg/kg/hour; loading: 0.4 mg/kg over 3 hours	
Treprostinil	0.625–1.25 ng/kg/minute; must be given in dedicated intravenous line	
Anesthetic/analgesia agents		
Acetaminophen	10–15 mg/kg IV Q6 H	
Dexmedetomidine	0.25–0.75 µg/kg/hour	Loading: 0.25–1.0 µg/kg over 10 minutes
Etomidate	0.2–0.3 mg/kg	
Fentanyl	1–10 µg/kg	Infusion: 1–10 µg/kg/hour
Hydromorphone	0.005–0.015 mg/kg	Maximum single dose: 2 mg
Ibuprofen	10 mg/kg IV Q6–8H	
Ketamine	IV: 1–2 mg/kg IM: 5–10 mg/kg	
Ketorolac	0.5–1 mg/kg IV; 0.5 mg/kg/dose every 6 hours (max 30 mg/dose; 120 mg/day)	
Midazolam	0.03–0.1 mg/kg IV	
Morphine	0.05–0.2 mg/kg IV	
Remifentanil	0.025–2 µg/kg/min	Loading: 0.5–1 µg/kg IV
Sufentanil	0.1–0.3 µg/kg/hour	Loading: 1–2 µg/kg IV
Muscle relaxants (intubation dose) and reversal of neuromuscular blockade		
Atracurium	0.4–0.5 mg/kg IV	
Cisatracurium	0.1 mg/kg IV	
Pancuronium	0.1 mg/kg IV	
Rocuronium	0.6–1.2 mg/kg IV	
Succinylcholine	1–2 mg/kg IV; 4 mg/kg IM	
Vecuronium	0.08–0.1 mg/kg IV	
Neostigmine	50–70 µg/kg IV	
Glycopyrrolate	10–14 µg/kg IV (with neostigmine)	
Sugammadex [12]*	Immediate reversal of rocuronium: 16 mg/kg Deep block (1–2 post-tetanic counts and prior to the second twitch following train-of-four stimulation): 4 mg/kg Moderate block (after appearance of the second twitch following TOF stimulation): 2 mg/kg	
Antibiotics		
Ampicillin	50 mg/kg IV (max 2 g)	
Cefazolin	25–30 mg/kg IV (max 1 g)	
Cefuroxime	25–50 mg/kg IV (max 1.5 g)	
Clindamycin	10–13 mg/kg IV (max 900 mg)	
Gentamicin	1–2.5 mg/kg IV (max 120 mg)	
Nafcillin	37.5–50 mg/kg IV (max 2 g)	
Piperacillin/tazobactam	50–100 mg/kg IV piperacillin component (max 16 g piperacillin component/day)	
Vancomycin	10–15 mg/kg IV (max 1 g)	

Antiemetics	
Dexamethasone	0.15–0.5 mg/kg IV
Metaclopromide	0.1–0.2 mg/kg/dose IV every 6–8 hours as needed (max. 10 mg)
Ondansetron	0.1 mg/kg IV (max. 4 mg)
Corticosteroids	
Dexamethasone	Airway edema: 0.25–0.5 mg/kg IV
Hydrocortisone	Adrenal insufficiency (stress dose): 50–100 mg/m^2/dose IV Anaphylaxis 0.5–2 mg/kg (max 250 mg)
Methylprednisolone	20–30 mg/kg IV bolus or to bypass circuit
Diuretics	
Bumetanide	0.1 mg/kg/dose (IV or PO)
Furosemide	0.5–1 mg/kg IV (max 20 mg)
Mannitol	0.25–2 g/kg IV
Antifibrinolytics	
Tranexamic acid [13, 14]	Neonate 0–2 mo.: 15 mg/kg bolus; 20 mcg/mL of CPB prime; 2.5 mg/kg/hour. infusion. Infant 2–12 mo.: 9 mg/kg bolus; 20 mcg/mL of CPB prime; 2 mg/kg/hour infusion. Child > 12 mo.: 4 mg/kg bolus; 20 mcg/mL of CPB prime; 2 mg/kg/hour infusion.
Aprotinin[a]	28,000–60,000 KIU/kg bolus; 28,000–60,000 KIU/kg to CPB prime, 3,500–7,000 KIU/kg/hour infusion
Epsilon aminocaproic acid [15]	Neonate 0–2 mo.: 40 mg/kg bolus; 0.1 mg/ml of CPB prime; 30 mg/kg/hour infusion. Infant 2–12 mo. and child > 12 mo.: 75 mg/kg bolus; 75 mg/kg for CPB prime; 75 mg/kg/hour infusion.
Anticoagulants and reversal	
Bivalirudin [16, 17]	For bypass: 1 mg/kg IV bolus; additional bolus of 0.1–0.5 mg/kg for subtherapeutic ACT; 50 mg to bypass circuit; infusion 2.5 mg/kg/hour For ECMO or VAD: 0.1–0.2 mg/kg bolus; infusion 0.03–0.3 mg/kg/hour; monitor PTT hepzyme
Heparin	300–400 units/kg (3–4 mg/kg) for CPB; 100 units/kg (1 mg/kg) for heparinization for non-CPB cases (e.g. coarctation of the aorta, systemic-to-pulmonary artery shunt)
Protamine	1–1.3 times heparin dose in mg
Electrolytes	
Sodium bicarbonate	1 mEq/kg; dilute 1 : 1 with sterile water for neonates
THAM (tromethamine)	1 mL/kg IV of 0.3 M solution; subsequent dosing based on blood gas result
Potassium chloride	0.5–1 mEq/kg IV over 1 hour
Magnesium sulfate	25–50 mg/kg IV over 1 hour
Dextrose	For the treatment of hypoglycemia D_{10}: 3–5 mL/kg IV for neonates D_{25}: 1–2 mL/kg IV for age 3 months to 2 years D_{50}: 0.5–1 mL/kg IV for age > 2 years
Miscellaneous drugs	
Diphenhydramine	For acute hypersensitivity 1–2 mg/kg IV (max. 50 mg/dose)
Flumazenil	1–5 µg/kg IV; repeat as necessary
Levoalbuterol	4–8 puffs MDI through ETT; may repeat
Naloxone	1–10 µg/kg IV; repeat as necessary
Ranitidine	1 mg/kg IV

Oral/intranasal premedications	
Dexmedetomidine	Intranasal: 2 μg/kg
Ketamine	Oral: 5–10 mg/kg
Midazolam	Intranasal: 0.2 mg/kg over 15 seconds, may repeat in 5–15 minutes (max 15 mg) Oral: 0.5–1 mg/kg
Pentobarbital	Oral: 3–5 mg/kg

Maximum doses of local anesthetics[b]

Drug	Spinal	Caudal/Lumbar epidural	Peripheral	Subcutaneous
Chlorprocaine	NA	8 mg/kg	8 mg/kg	8 mg/kg
Chlorprocaine with epinephrine 1 : 200 K	NA	10 mg/kg	10 mg/kg	10 mg/kg
Tetracaine	0.2–0.6 mg/kg	NA	NA	NA
Lidocaine (0.5–1% infiltration), (1–2% peripheral, epidural, subcutaneous), (5% spinal)	1–2.5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg
Lidocaine with epinephrine 1 : 200 K	1–2.5 mg/kg	7 mg/kg	7 mg/kg	7 mg/kg
Bupivacaine (0.125–0.5% infiltration), (0.25–5% peripheral, epidural, subcutaneous)	0.3–0.5 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
Bupivacaine with epinephrine 1 : 200 K	0.3–0.5 mg/kg	3 mg/kg	3 mg/kg	3 mg/kg
Ropivacine (0.2–0.9% peripheral, epidural)	NA	2 mg/kg	2 mg/kg	2 mg/kg
Ropivacine with epinephrine	NA	3 mg/kg	3 mg/kg	3 mg/kg
Prilocaine (1–2% peripheral), (2–3% epidural)	NA	5 mg/kg	5 mg/kg	5 mg/kg
Liposomal Bupivacine 1.3%	NA	NS	NA	3 mg/kg

Local anesthesthetic toxicity treatment	
20% Lipid emulsion [18]	Under 70 kg: Bolus 1.5 mL/kg over 2–3 minutes, start infusion at 0.25 mL/kg/hour; If patient remains unstable, repeat bolus and double infusion rate, max dose 12 mL/kg Over 70 kg: Bolus 100 mL over 2–3 minutes, infuse 250 mL over 15–20 minutes; If patient remains unstable, repeat bolus and double infusion, max dose 12 mL/kg

Blood products and volume expanders	
Albumin 5%	10–20 mL/kg IV
Anti-inhibitor coagulant complex (FEIBA®; activated prothrombin complex concentrate) [19, 20]	50–100 units/kg; maximum rate of infusion 2 units/kg/min 10 units/kg IV, may repeat dose
Cryoprecipitate	15 mL/5–10 kg IV
Fibrinogen concentrate [21]	60–70 mg/kg when fibrinogen level is not known; when fibrinogen level is known Dose (mg/kg) = [100 (mg/dL) – measured level (mg/dL)] divided by 1.7
Fresh frozen plasma	10–20 mL/kg IV
Packed red blood cells	10–15 mL/kg IV
Platelets	1 random unit/5 kg will increase platelet count by 50,000; 1 pheresis unit = 6 random units
Prothrombin complex concentrate (Octaplex®, Kcentra®)	Pretreatment INR 2- < 4: Administer 25 units/kg (max dose 2,500 units); Pretreatment INR 4–6: Administer 35 units/kg (max dose 3,500 units); Pretreatment INR > 6: Administer 50 units/kg (max dose 5,000 units)

Recombinant factor VIIa [19]	40–60 µg/kg IV; may repeat dose q 1–2 hours (max. Three total doses)
Whole blood	10–15 mL/kg IV
DC defibrillation/synchronized cardioversion	
Internal defibrillation	2 J, increase to 5 J, 10 J
External defibrillation	2–5 J/kg; increase if ineffective to max 200 J
External synchronized cardioversion	0.5 J/kg; increase if ineffective to 1 J/kg

[a] Aprotinin was not available in the USA as of December 2007.

[b] TCH EPIC dose calculator, September 2022.

References

1 Tobias JD, Schechter WS, Phillips A, et al. Clevidipine for perioperative blood pressure control in infants and children undergoing cardiac surgery for congenital heart disease. J Pediatr Pharmacol Ther 2011;16:55–60.

2 Ricci Z, Garisto C, Favia I, et al. Levosimendan infusion in newborns after corrective surgery for congenital heart disease: randomized controlled trial. Intensive Care Med 2012;38:1198–204.

3 Chowdhury D, Ojamaa K, Parnell VA, et al. A prospective randomized clinical study of thyroid hormone treatment afteroperations for complex congenital heart disease. J Thorac Cardiovasc Surg 2001;122:1023–5.

4 Mackie AS, Booth KL, Newburger JW, et al. A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. J Thorac Cardiovasc Surg 2005;130:810–6.

5 Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thoracic Surg 2010;22:140–4.

6 Bhalla T, Sawardekar A, Russell H, Tobias JD. The role of methylene blue in the pediatric patient with vasoplegic syndrome. World J Pediatr Congenit Heart Surg 2011;2:652–5.

7 Shanmugam G. Vasoplegic syndrome – the role of methylene blue. Eur J Cardiothorac Surg 2005;28:705–10.

8 Dahlem P, van Aalderen WM, de Neef M, et al. Randomized controlled trial of aerosolized prostacyclin therapy in children with acute lung injury. Crit Care Med 2004;32(4):1055–60.

9 Limsuwan A, Wanitkul S, Khosithset A, et al. Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol 2008;129(3):333–8.

10 Steinhorn RH, Kinsella JP, Pierce C, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. J Pediatr 2009;155:841–7.

11 Stocker C, Penny DJ, Brizard CP, et al. Intravenous sildenafil and inhaled nitric oxide: a randomized trial in infants after cardiac surgery. Intensive Care Med 2003;29:1996–2003.

12 Geldner G, Niskanen M, Laurila P, et al. A randomised controlled trial comparing sugammadex and neostigmine at different depths of neuromuscular blockade in patients undergoing laparoscopic surgery. Anaesthesia 2012;67(9):991–8.

13 Grassin-Delyle S, Couturier R, Abe E, et al. A practical tranexamic acid dosing scheme based on population pharmacokinetics in children undergoing cardiac surgery. Anesthesiology 2013;118:853–62.

14 Wesley MC, Pereira LM, Scharp LA, et al. Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2015;122:746–58.

15 Eaton MP, Alfieris GM, Sweeney DM, et al. Pharmacokinetics of epsilon-aminocaproic acid in neonates undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2015;122:1002–9.

16 Almond CSD, Harrington J, Thiagarajan R, et al. Successful use of bivalirudin for cardiac transplantation in a child with heparin-induced thrombocytopenia. J Heart Lung Transplant 2006;25:1376–9.

17 Ahmed M, Adachi I, Teruya J. Chapter 59: Anticoagulation. In: Mery CM, Bastero P, Hall SR, et al. (eds) The Texas Children's Hospital Handbook of Congenital Heart Disease, Houston, TX: Texas Children's Hospital, 2020, p. 447.

18 Neal JM, Neal J, Weinberg GL. American society of regional anesthesia and pain management local anesthetic systemic toxicity checklist: 2020 version. Reg Anesth Pain Med 2021;46:81–2.

19 Carroll RB, Zaki H, McCracken C, et al. Use of factor viia amd anti-inhibitor coagulant complex in pediatric cardiac surgery patients. J Pediatr Pharmacol Ther 2020; 25:540–6.

20 Maeda K, Asija R, Hollander S, et al. Low dose factor eight inhibitor bypassing activity (FEIBA) for incessant bleeding in pediatric patients on mechanical circulatory support (MCS). J Heart and Lung Transplantation 2013;32:S290.

21 Galas FR, de Almeida JP, Fukushima JP, et al. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial. J Thorac Cardiovasc Surg 2014;148:1647–55.

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